Direct approaches to natural product synthesis

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Direct approaches to natural product synthesis

by

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A dissertation submitted to the graduate faculty
in partial fulfillment of the requirements for the degree of
DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

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Ames, Iowa
2003
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GENERAL INTRODUCTION

Over the last decades, organic synthesis has flourished with the discovery and invention of new synthetic strategies and technologies. Especially, these novel methods allow us to access complex natural products in an efficient way. Likewise, the design of direct approaches to complex molecules almost always prompts us to develop new methodologies.

Syntheses of biologically active natural products and their analogs have become an important tool in search of new drugs. Approaches to these molecules in a concise manner are highly desirable.

In this context, we investigated direct routes to several biologically important natural products. During the syntheses, novel synthetic methodologies were developed. These studies will be useful to design approaches to other structurally related natural products.
CHAPTER 1. SYNTHETIC APPROACH TO MALIBATOL A

Introduction

Malibatol A and several other structurally related oligostilbenes were isolated from the organic extract of the leaves of *Hopea malibato* by Boyd and coworkers in 1998.\(^1\)
While malibatols A and B exhibited cytotoxicity to the host cells (CEM SS) in the antiviral assay, dibalanocarpol and balanocarpol showed very modest HIV-inhibitory activity. Shoreaphenol or hopeafuran was also isolated from the bark of Shorea robusta or the stem wood of Hopea utilis. In addition, structures of several novel oligostilbenes were determined recently. Despite their interesting biological activities as well as their unique carbon framework, no synthetic approach toward these types of compounds had been reported.

In the course of our synthetic studies towards isoflavanquinones, we observed an interesting reaction in which a metal-halogen exchange using alkyl lithium reagents was faster than the reaction with a carbonyl group. Thus, instead of a product which resulted from a direct addition of methyl lithium to a carbonyl group, benzofuran compound 2 was obtained in good yield from 1. The mechanism involved the attack of an aryl lithium species (which was formed via fast metal-halogen exchange) to a carbonyl group followed by the loss of water.

Since many oligostilbenes possess a benzofuran moiety as part of their structures, we decided to apply this new benzofuran preparation method to the synthesis of these natural products.
Results and Discussion

Synthetic target 3 was chosen to validate our strategy. We envisioned that a seven-membered ring could be constructed via regioselective epoxide opening, as illustrated in the retrosynthetic scheme. We expected that benzofuran moiety could be produced employing our novel benzofuran formation strategy.

\[
\begin{array}{c}
\text{MeO} \\
\text{MeO} \\
\text{OMe} \\
\text{MeO}
\end{array}
\quad \quad
\begin{array}{c}
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\end{array}
\]

We began our study with iodo aldehyde 5, which had been prepared by Lock from 3-hydroxybenzaldehyde in one step.\(^6\)

\[
\begin{align*}
&\text{CHO} \\
&\text{OH}
\end{align*}
\quad \quad
\begin{align*}
&\text{CHO} \\
&\text{OH}
\end{align*}
\]

1) Hg(OAc)\(_2\), AcOH, H\(_2\)O/\(\text{EtOH}, 100^\circ\text{C}\)  
2) I\(_2\), KI, H\(_2\)O, 70^\circ\text{C}

Iodo aldehyde 5 was treated with benzyltriphenylphosphonium chloride in the presence of \(n\)-BuLi to provide compound 6 as a 1:1 E/Z mixture in 90-95% yield. Phenol 6 was then alkylated with bromoketone 7\(^7\) and potassium carbonate in boiling acetone to give ketone 8 in quantitative yield. Reaction of ketone 8 with 3 equivalents of MeLi at \(-78^\circ\text{C}\) followed by the treatment with PTSA at room temperature afforded benzofuran 9 in 74% yield.
With this benzofuran 9 in hand, we next directed our efforts to make either an epoxide or a...
similarly reactive intermediate to initiate seven-membered ring formation. Unfortunately, none of these approaches provided the desired product.

By the same sequence, we also made a para-methoxyphenyl analog. Interestingly, cis- and trans-products were separated from the Wittig adduct mixture to a great extent by simply suspending the mixture in n-hexane, filtering, and rinsing the solid with n-hexane. While the white solid contained the trans isomer as the major product, the liquid contained the cis isomer as the major product. Thus, we reacted the cis isomer 11a and the trans isomer 11b separately, with bromoketone 7 and potassium carbonate in boiling acetone. Reaction of adducts 12a and 12b with MeLi and subsequent PTSA treatment led to benzofurans 13a and 13b, respectively, in good yields.

With the trans isomer 13b in hand, we carried out epoxidation and dihydroxylation. However, both experiments gave a complex mixture.
At this stage, we suspected that the benzofuran unit might prevent the desired transformation from occurring. Therefore, we subjected 12b to the same reaction conditions for 13b. Unfortunately, this wasn’t successful, either.
The results described above forced us to modify the original strategy. Thus, we decided to install the epoxide functionality within molecule in a different manner.

Aldehyde of 5 was protected as the acetal with trimethyl orthoformate and PTSA in boiling methanol. Phenol 14 and bromoketone 7 were coupled in the presence of potassium periodinane.
carbonate in boiling acetone to afford ketone 15 in quantitative yield. Iodo ketone 15 was treated with MeLi at —78 °C followed by exposure of the resulting mixture to PTSA at ambient temperature to give benzofuran carboxaldehyde 16 in 75% yield. One of the methods to make an epoxide from an aldehyde is the sulfonium chemistry developed by Corey. Thus, treatment of aldehyde 16 with dimethyl para-methoxybenzylsulfonium chloride 17° and potassium tert-butoxide in THF at room temperature delivered epoxide 4 as a single stereoisomer as evidenced by proton NMR spectroscopy. The small coupling constant (J = 1.8 Hz) of the hydrogens attached to the epoxide ring supported the assigned structure. This epoxide 4 now set the stage for the crucial 7-membered ring formation. Gratifyingly, exposure of epoxide 4 in a catalytic amount of SnCl₄ at —78 °C provided benzylic alcohol 3 as a single compound in 76% yield. The coupling constant between the two methine protons in 3 was 2.7 Hz, compared to 2.5 Hz in malabatol A. 2D NMR analysis supported a trans relationship between the methine proton and the hydroxyl group.¹⁰

We expected that the para-methoxyphenyl group would direct the epoxide opening. However, we could not rule out the isomeric alcohol 19. Oxidation of the alcohol 3 with the Dess-Martin periodinane reagent gave a ketone that we assigned as 18 based on the deshielding of the hydrogen at C-5 of the benzofuran. The chemical shifts of the hydrogens on the para-methoxyphenyl group were not deshielded after the oxidation. Moreover, the mass spectra did not exhibit fragmentation that one would expect for alcohol 19 (M⁺ - 137) or the ketone derived from oxidation of 19 (M⁺ - 135).

Reduction of ketone 18 with either sodium borohydride in methanol or DIBAL in THF provided only alcohol 3. The tetracyclic ring system in 18 is flat with the para-methoxyphenyl group approximately perpendicular to the ring system. Hydride attack
opposite to the \textit{para}-methoxyphenyl group would explain the production of 3.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\includegraphics[width=0.4\textwidth]{image.png}};
\node (b) at (4,0) {NaBH$_4$, MeOH \hfill \includegraphics[width=0.4\textwidth]{image.png}};
\node (c) at (4,0) {0 °C, 100\% \hfill or DIBAL, THF \hfill 0 °C, 100\%};
\end{tikzpicture}
\end{center}

In conclusion, we developed a concise synthetic route to the malibatol A ring system and structurally related oligostilbenes, featuring a novel construction of a benzofuran ring and an efficient generation of a seven-membered ring by regio- and stereoselective epoxide opening. This route should enable us to construct malibatol A and several analogs.

\textbf{Experimental Section}

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane and benzene were distilled over calcium hydride. All experiments were performed under argon atmosphere unless otherwise noted. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or Bruker 400 MHz instrument. All chemical shifts are reported relative to CDCl$_3$ (7.26 ppm for $^1$H and 77.06 ppm for $^{13}$C), unless otherwise noted. Coupling constants ($J$) are reported in Hz with abbreviations: $s =$ singlet, $d =$ doublet, $t =$ triplet, $q =$ quartet, $m =$ multiplet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer and low resolution mass spectra were performed with a Finnegan 4023 mass spectrometer. Standard grade silica gel (60 A, 32-63 μm) was used for a flash column chromatography.
2-(2-Iodo-5-methoxyphenoxy)-1-(2,4,5-trimethoxyphenyl)ethanone (1)

Preparation and characterization data of 1 are described in Chapter 2 of this dissertation.

6-Methoxy-3-(2,4,5-trimethoxyphenyl)benzofuran (2)

To a solution of MeLi (1.4 M solution in THF, 337 µL, 0.471 mmol) in THF (2 mL) was dropwise added a solution of ketone 1 (72 mg, 0.157 mmol) in THF (4 mL + 1 mL for rinse) at -78 °C via cannula. After being stirred at -78 °C for 5 min, the mixture was quenched with saturated NH₄Cl at -78 °C. The mixture was concentrated in vacuo. The residue was diluted with CH₂Cl₂ and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated to dryness. The resulting residue was purified by sgc (H:EA = 2:1) to give benzofuran 2 (45 mg, 91%). 300 MHz ¹H NMR (CDCl₃) δ 7.82 (1H, s), 7.58 (1H, d, J = 8.7 Hz), 7.26 (1H, s), 7.06 (1H, d, J = 2.1 Hz), 6.92 (1H, dd, J = 8.7, 2.4 Hz), 6.68 (1H, s), 3.96 (3H, s), 3.91 (3H, s), 3.87 (3H, s), 3.83 (3H, s); 75 MHz ¹³C NMR (CDCl₃) δ 158.1, 156.4, 151.6, 149.2, 143.4, 142.6, 121.3, 120.9, 117.5, 114.0, 112.8, 112.0, 98.6, 96.3, 57.0, 56.7, 56.4, 56.0; HRMS m/z for C₁₉H₁₅O₂ calcd 314.1154, found 314.1160.

3-Hydroxy-2-iodobenzaldehyde (5)

To a solution of 3-hydroxybenzaldehyde (10 g, 81.9 mmol) in EtOH (40 mL) were added Hg(OAc)₂ (26 g, 81.9 mmol), H₂O (40 mL), and AcOH (1.2 mL) at rt. The mixture was heated at 100 °C overnight. After being cooled to rt, the mixture was evaporated to remove EtOH. The residue was suction-filtered and the solid was washed with H₂O a couple of times. The solid (not completely dried) was mixed with a solution of KI (47 g, 393.1 mmol) and I₂ (30 g, 163.8 mmol) in H₂O (200 mL). After being heated at 70 °C for 2 h, the mixture was cooled to rt. Excess aqueous NaHSO₃ solution was added to it to decolorize. The mixture was extracted with ethyl acetate two times. The organic layer was washed with H₂O
and brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The resulting residue was passed through a short silica gel column, eluting with solvent (H:EA = 2:1). The eluted solvent was concentrated and the residue was suspended in benzene. Then, it was filtered and washed with benzene. A yellow solid was obtained. To increase the yield, the filtrate was concentrated, suspended in benzene, and filtered again. 300 MHz ¹H NMR (acetone-d₆) δ 10.14 (1H, d, J = 1.8 Hz), 9.64 (1H, br s), 7.42-7.30 (2H, m), 7.30-7.20 (1H, m)

2-Iodo-3-styrylphenol (6)

To a suspension of benzyltriphenylphosphonium chloride (3.24 g, 8.34 mmol) in THF (20 mL) was added n-BuLi (2.5 M solution in hexanes, 2.78 mL, 6.95 mmol) dropwise at -78 °C. After being stirred for 15 min at rt, the mixture was recooled to -78 °C. To this mixture was transferred a solution of 5 (688 mg, 2.78 mmol) in THF (10 mL + 5 mL for rinse) at -78 °C via cannula. After being stirred at rt for 30 min, the mixture was quenched with saturated NH₄Cl at 0 °C. The organic solvent was evaporated. The residue was diluted with CH₂Cl₂ and washed with 10% HCl. The aqueous layer was extracted with CH₂Cl₂ one more time. The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by sgc (H:EA = 3:1) to give 6 (850 mg, 95%) as a 1:1 cis:trans mixture. 300 MHz ¹H NMR (CDCl₃) δ 7.65-6.45 (10H, m), 5.69 and 5.65 (1H, s).

2-Bromo-1-(3,4,5-trimethoxyphenyl)ethanone (7)

To a solution of 3',4',5'-trimethoxyacetophenone (3.57 g, 16.98 mmol) in ethyl acetate (28 mL) and CHCl₃ (28 mL) was added CuBr₂ (7.59 g, 33.96 mmol) at rt. After being heated at 85 °C for 10 h, the mixture was cooled to rt. The mixture was filtered through Celite and washed with CH₂Cl₂. The filtrate was concentrated in vacuo. The residue was suspended in
solvent (H:EA = 3:1), filtered, and rinsed with small amount of solvent (H:EA = 3:1). The solid 7 (2.9 g) was dried under reduced pressure. The filtrate was concentrated and the resulting residue was purified by sgc (H:EA = 5:1 to 3:1) to give 7 (780 mg, total yield: 75%).

300 MHz \( ^1H \) NMR (CDCl\(_3\)) \( \delta \) 7.24 (2H, s), 4.41 (2H, s), 3.94 (3H, s), 3.93 (6H, s).

2-(2-Iodo-3-styrylphenoxy)-1-(3,4,5-trimethoxyphenyl)ethanone (8)

To a solution of 6 (698 mg, 2.168 mmol) and 7 (627 mg, 2.168 mmol) in acetone (7.2 mL) was added \( \text{K}_2\text{CO}_3 \) (300 mg, 2.168 mmol). The reaction mixture was heated to reflux for 2 h. After being cooled to rt, the solvent was evaporated under reduced pressure. The residue was diluted with CH\(_2\)Cl\(_2\) and washed with H\(_2\)O and brine, successively. The organic layer was dried over MgSO\(_4\), filtered, and evaporated to afford 8 (1.149 g, 100%). 300 MHz \( ^1H \) NMR (CDCl\(_3\)) \( \delta \) 7.62-6.48 (12H, m), 5.28 and 5.26 (2H, s), 3.94 (6H, s), 3.93 (3H, s).

4-Styryl-3-(3,4,5-trimethoxyphenyl)benzofuran (9)

To a solution of MeLi (1.4 M solution in THF, 6.5 mL, 9.13 mmol) in THF (12 mL) was added a solution of 8 (968 mg, 1.826 mmol) in THF (8 mL + 4 mL for rinse) at \(-78^\circ\)C via cannula. After being stirred at rt for 10 min, the mixture was quenched with saturated NH\(_4\)Cl. The organic solvent was evaporated in vacuo. The residue was diluted with CH\(_2\)Cl\(_2\) and washed with brine. The organic layer was dried over MgSO\(_4\), filtered, and evaporated to dryness. The intermediate benzylic alcohol was purified by sgc (H:EA = 3:1) for NMR data. 300 MHz \( ^1H \) NMR (CDCl\(_3\)) \( \delta \) 7.35-6.14 (12 H, m), 4.61 and 4.55 (2H, d, \( J = 10.2 \) Hz), 3.83 (3H, s), 3.80 (3H, s), 3.77 (3H, s).

The crude mixture was dissolved in benzene (10 mL) and MeOH (5 mL). PTSA-H\(_2\)O (325 mg, 1.709 mmol) was added to this solution at rt. After being stirred at rt for 3 h, the solvent was evaporated. The residue was diluted with CH\(_2\)Cl\(_2\) and washed with brine. The
organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 5:1) to give 9 (520 mg, 74%). 300 MHz ¹H NMR (CDCl₃) δ 7.70-6.40 (13H, m), 3.96 and 3.92 (3H, s), 3.78 and 3.75 (6H, s); HRMS m/z for C₂₅H₂₂O₄ calcd 386.1518, found 386.1525.

(4-Methoxybenzyl)triphenylphosphonium chloride (10)

A mixture of 4-methoxybenzyl chloride (6.78 g, 43.29 mmol) and triphenylphosphine (11.36 g, 43.29 mmol) in toluene (54 mL) was heated to reflux overnight. After being cooled to rt, the white salt was filtered, washed with toluene a couple of times, and dried under reduced pressure.

2-Iodo-3-[2-(4-methoxyphenyl)vinyl]phenol (11a/b)

To a suspension of 4-methoxybenzyltriphenylphosphonium chloride (7.6 g, 18.153 mmol) in THF (44 mL) was added n-BuLi (2.5 M solution in hexanes, 6.051 mL, 15.128 mmol) at 0 °C. After being stirred at rt for 15 min, the mixture was recooled to 0 °C. To this mixture was transferred a solution of 5 (1.5 g, 6.051 mmol) at 0 °C. After being stirred at rt for 20 min, the mixture was quenched with saturated NH₄Cl at 0 °C. The organic solvent was evaporated. The residue was diluted with CH₂Cl₂ and washed with 10% HCl. The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by sgc (H:EA = 4:1 to 3:1) to afford a cis/trans mixture (1.6 g, 75%). This mixture was suspended in n-hexane. The solid was filtered and washed with n-hexane. The white solid contained the trans isomer as the major product. The filtrate was evaporated to dryness to give an oil which contained the cis isomer as the major product.

11a (cis): 300 MHz ¹H NMR (CDCl₃) δ 7.15-7.03 (3H, m), 6.89 (1H, dd, J = 8.1, 0.6 Hz), 6.82 (1H, d, J = 7.5 Hz), 6.74 (2H, d, J = 8.7 Hz), 6.59 (1H, d, J = 12.3 Hz), 6.40 (1H, d, J =
12.0 Hz), 5.69 (1H, br s), 3.77 (3H, s).

11b (trans): 300 MHz $^1$H NMR (CDCl$_3$) δ 7.49 (2H, d, $J = 8.7$ Hz), 7.26-7.08 (3H, m), 6.99-6.85 (4H, m), 5.51 (1H, s), 3.85 (3H, s).

2-{2-Iodo-3-[2-(4-methoxyphenyl)vinyl]phenoxy}-1-(3,4,5-trimethoxyphenyl)ethanone
(12a) (cis isomer)

To a solution of 11a (548 mg, 1.557 mmol) and 7 (450 mg, 1.557 mmol) in acetone (5 mL) was added K$_2$CO$_3$ (215 mg, 1.557 mmol). The reaction mixture was heated to reflux for 1 h. After being cooled to rt, the solvent was evaporated under reduced pressure. The residue was diluted with CH$_2$Cl$_2$ and washed with H$_2$O and brine, successively. The organic layer was dried over MgSO$_4$, filtered, and evaporated to afford 12a (872 mg, 100%). 300 MHz $^1$H NMR (CDCl$_3$) δ 7.36 (2H, s), 7.08 (1H, d, $J = 7.0$ Hz), 7.03 (2H, d, $J = 8.4$ Hz), 6.84 (1H, d, $J = 6.9$ Hz), 6.69 (2H, d, $J = 9$ Hz), 6.61 (1H, d, $J = 8.1$ Hz), 6.56 (1H, d, $J = 12.0$ Hz), 6.40 (1H, d, $J = 12.0$ Hz), 5.27 (2H, s), 3.93 (9H, s), 3.75 (3H, s).

2-{2-Iodo-3-[2-(4-methoxyphenyl)vinyl]phenoxy}-1-(3,4,5-trimethoxyphenyl)ethanone
(12b) (trans isomer)

The same procedure for 12a was applied. 300 MHz $^1$H NMR (CDCl$_3$) δ 7.50 (2H, d, $J = 9.0$ Hz), 7.36 (2H, s), 7.40-6.60 (5H, m), 6.92 (2H, d, $J = 9.0$ Hz).

4-[2-(4-Methoxyphenyl)vinyl]-3-(3,4,5-trimethoxyphenyl)benzofuran (13a) (cis isomer)

To a solution of MeLi (1.4 M solution in THF, 8.0 mL, 11.24 mmol) in THF (15 mL) was added a solution of 12a (1.259 g, 2.248 mmol) in THF (10 mL + 3 mL for rinse) at -78 °C via cannula. After being stirred at rt for 10 min, the mixture was quenched with saturated NH$_4$Cl. The organic solvent was evaporated in vacuo. The residue was diluted with CH$_2$Cl$_2$ and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated to
dryness. The crude mixture was dissolved in benzene (10 mL) and MeOH (5 mL). PTSA-
H$_2$O (428 mg, 2.25 mmol) was added to this solution at rt. After being stirred at rt for 3 h, the
solvent was evaporated. The residue was diluted with CH$_2$Cl$_2$ and washed with brine. The
organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was
purified by sgc (H:EA = 5:1) to give 13a (674 mg, 72%). 300 MHz $^1$H NMR (CDCl$_3$) δ 7.61
(1H, s), 7.42 (1H, dd, $J = 6.6, 2.7$ Hz), 7.23-7.14 (2H, m), 7.05 (2H, d, $J = 8.7$ Hz), 6.66 (2H,
d, $J = 9.0$ Hz), 6.61 (2H, s), 6.48 (1H, d, $J = 12.3$ Hz), 6.37 (1H, d, $J = 12.0$ Hz), 3.92 (3H, s),
3.77 (6H, s), 3.73 (3H, s); 75 MHz $^{13}$C NMR (CDCl$_3$) δ 158.9, 156.2, 152.8, 142.4, 137.6,
132.1, 130.4, 130.0, 129.7, 127.8, 127.0, 124.8, 124.7, 124.3, 123.9, 113.7, 110.7, 107.2, 61.2,
56.1, 55.3; HRMS m/z for C$_{26}$H$_{24}$O$_5$ calcd 416.1624, found 416.1629.

4-[2-(4-Methoxyphenyl)vinyl]-3-(3,4,5-trimethoxyphenyl)benzofuran (13b) (trans
isomer)

The same procedure for 13a was applied. 300 MHz $^1$H NMR (CDCl$_3$) δ 7.62 (1H, s),
7.52 (1H, d, $J = 7.5$ Hz), 7.42 (1H, d, $J = 8.1$ Hz), 7.33 (1H, d, $J = 8.1$ Hz), 7.19 (1H, d, $J =
16.2$ Hz), 7.12 (2H, d, $J = 8.7$ Hz), 6.95 (1H, d, $J = 16.5$ Hz), 6.79 (2H, d, $J = 8.7$ Hz), 6.74
(2H, s), 3.94 (3H, s), 3.79 (3H, s), 3.75 (6H, s); HRMS m/z for C$_{26}$H$_{24}$O$_5$ calcd 416.1624,
found 416.1629.

3-Dimethoxymethyl-2-iodophenol (14)

To a solution of 5 (342 mg, 1.38 mmol) in MeOH (5 mL) were added trimethyl
orthoformate (377 µL, 3.45 mmol) and PTSA-H$_2$O (26 mg, 0.14 mmol) at rt. The mixture
was heated to reflux overnight. The solvent was evaporated in vacuo. The residue was diluted
with ethyl acetate and washed with saturated NaHCO$_3$ solution and brine, successively. The
organic layer was dried over MgSO$_4$, filtered, and evaporated to dryness. The crude residue
(405 mg, 100%) was pure enough to run the next step. 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.24 (1H, t, $J$ = 7.8 Hz), 7.12 (1H, dd, $J$ = 7.8, 1.8 Hz), 7.00 (1H, dd, $J$ = 7.8, 1.5 Hz), 5.59 (1H, s), 5.34 (1H, s), 3.37 (6H, s); 100 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 155.2, 140.4, 129.3, 120.2, 115.4, 106.7, 89.7, 60.8, 53.9.

2-(3-Dimethoxymethyl-2-iodophenoxy)-1-(3,4,5-trimethoxyphenyl)ethanone (15)

To a solution of 14 (1.123 g, 3.82 mmol) and 7 (1.1 g, 3.82 mmol) in acetone (13 mL) was added K$_2$CO$_3$ (792 mg, 5.73 mmol). The reaction mixture was heated to reflux for 4 h. After being cooled to rt, the solvent was evaporated under reduced pressure. The residue was diluted with CH$_2$Cl$_2$ and washed with H$_2$O and brine, successively. The organic layer was dried over MgSO$_4$, filtered, and evaporated to afford 15 (1.917 g, 100%). 400 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.23 (2H, s), 7.22-7.09 (2H, m), 6.69 (1H, d, $J$ = 7.6 Hz), 5.38 (1H, s), 5.21 (2H, s), 3.84 (9H, s), 3.31 (6H, s); 100 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 193.3, 156.7, 153.2, 143.3, 141.9, 129.4, 129.0, 121.3, 112.7, 107.0, 106.0, 90.9, 72.5, 60.9, 56.4, 54.2, 53.6.

3-(3,4,5-Trimethoxyphenyl)benzofuran-4-carbaldehyde (16)

To a solution of MeLi (1.4 M solution in THF, 15.0 mL, 21.2 mmol) in THF (25 mL) was added a solution of 15 (2.13 g, 4.24 mmol) in THF (10 mL + 5 mL for rinse) at -78 °C via cannula. After being stirred at rt for 10 min, the mixture was quenched with saturated NH$_4$Cl. The organic solvent was evaporated in vacuo. The residue was diluted with CH$_2$Cl$_2$ and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated to dryness to give crude intermediate (1.6 g, 100%). The intermediate benzy alcohol was identified in crude $^1$H NMR. 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.32 (1H, d, $J$ = 7.8 Hz), 7.07 (1H, dd, $J$ = 7.8, 0.9 Hz), 6.96 (1H, d, $J$ = 8.1 Hz), 6.63 (2H, s), 4.98 (1H, s), 4.69 (1H, d, $J$ = 9.9 Hz), 4.47 (1H, d, $J$ = 1.2 Hz), 4.39 (1H, dd, $J$ = 9.9, 1.5 Hz), 3.84 (3H, s), 3.79 (6H, s), 3.29
The crude mixture (1.5 g, 3.99 mmol) was dissolved in acetone (22 mL). PTSA-H$_2$O (759 mg, 3.99 mmol) was added to this solution at rt. After being stirred at rt for 7 h, the solvent was evaporated. The residue was diluted with CH$_2$Cl$_2$ and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 5:1 to 3:1) to give 16 (934 mg, 75%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 10.24 (1H, d, $J$ = 0.6 Hz), 7.88 (1H, dd, $J$ = 7.5, 0.6 Hz), 7.75 (1H, dd, $J$ = 8.1, 0.6 Hz), 7.74 (1H, s), 7.43 (1H, t, $J$ = 8.1 Hz), 6.68 (2H, s), 3.89 (3H, s), 3.84 (6H, s); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 190.3, 156.2, 153.8, 144.7, 138.3, 130.4, 128.6, 128.2, 124.8, 122.9, 122.5, 117.5, 106.7, 61.2, 56.4; HRMS m/z for C$_{18}$H$_{16}$O$_{5}$ calcd 312.0998, found 312.1002.

(4-Methoxybenzyl)dimethylsulfonium chloride (17)

A mixture of 4-methoxybenzyl chloride (1.1 g, 7.02 mmol) and dimethyl sulfide (2.5 mL, 34.04 mmol) in CHCl$_3$ (10 mL) was stirred at rt for 3 days. The solvent was evaporated under reduced pressure. The residue was suspended in ethyl acetate and sonicated for 30 min. The liquid layer was decanted and the solid was suspended in ethyl acetate again. The suspension was suction-filtered rapidly and rinsed with ethyl acetate. White waxy solid was dried under reduced pressure. 300 MHz $^1$H NMR (D$_2$O) $\delta$ 7.25 (2H, d, $J$ = 8.4 Hz), 6.92 (2H, d, $J$ = 8.4 Hz), 4.39 (2H, s), 3.69 (3H, s), 2.58 (6H, s).

4-[3-(4-Methoxyphenyl)oxiranyl]-3-(3,4,5-trimethoxyphenyl)benzofuran (4)

To a suspension of 17 (1.38 g, 6.32 mmol) in THF (12 mL) was added t-BuOK (708 mg, 6.32 mmol) at 0 °C. After being stirred at rt for 1 h, the mixture was recooled to 0 °C. To this mixture was transferred a solution of 16 (492 mg, 1.58 mmol) in THF (12 mL + 5 mL for rinse) at 0 °C via cannula. After being stirred at rt for 3 h, the reaction mixture was quenched
with saturated NH₄Cl at 0 °C. The solvent was evaporated in vacuo. The residue was diluted with CH₂Cl₂ and washed with brine. The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by sgc (H:EA = 7:1) to afford 4 (627 mg, 92%) plus recovered starting material 15 (20 mg, 4%). 300 MHz ¹H NMR (CDCl₃) δ 7.58 (1H, s), 7.49 (1H, d, J = 8.4 Hz), 7.36 (1H, t, J = 7.8 Hz), 7.24 (1H, d, J = 7.5 Hz), 6.97 (2H, d, J = 8.7 Hz), 6.81 (2H, d, J = 8.4 Hz), 6.55 (2H, s), 4.09 (1H, d, J = 1.8 Hz), 3.80 (6H, s), 3.74 (1H, d, J = 1.8 Hz), 3.57 (6H, s); 75 MHz ¹³C NMR (CDCl₃) δ 160.2, 155.3, 153.2, 142.7, 137.9, 131.6, 128.7, 128.1, 127.1, 126.3, 125.2, 122.7, 118.3, 114.3, 111.4, 107.0, 63.5, 61.1, 59.2, 56.0, 55.6; HRMS m/z for C₂₆H₂₄O₆ calcd 432.1573, found 432.1580.

8,9,10-Trimethoxy-7-(4-methoxyphenyl)-6,7-dihydro-2-oxadibenzo[cd,h]azulen-6-ol (3)

1) from the reaction of 4 with SnCl₄:

To a solution of 4 (41.5 mg, 0.096 mmol) in CH₂Cl₂ (4.8 mL) was added SnCl₄ (1 M solution in CH₂Cl₂, 19 µL, 0.019 mmol) at -78 °C. After being stirred at -78 °C for 5 min, the mixture was quenched with saturated NH₄Cl at -78 °C. The mixture was diluted with CH₂Cl₂ and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA:CH₂Cl₂ = 5:1:1) to give 3 (31.5 mg, 76%).

2) from the reaction of 18 with NaBH₄ or DIBAL:

To a solution of 18 (8.9 mg, 0.021 mmol) in MeOH (1 mL) was added NaBH₄ (2 mg, 0.053 mmol) at 0 °C. After 5 min, the mixture was quenched with saturated NH₄Cl at 0 °C. After the mixture was concentrated in vacuo, the residue was diluted with CH₂Cl₂ and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in
vacuo to give 3 (8.9 mg, 100%). Alternatively, to a solution of 18 (10 mg, 0.023 mmol) in THF (1.5 mL) was added DIBAL (1 M solution in THF, 69 μL, 0.069 mmol) at 0 °C. After 5 min, the mixture was quenched with H2O at 0 °C. The mixture was filtered through Celite and rinsed with CH2Cl2. The filtrate was evaporated in vacuo to give 3 (10 mg, 100%). 300 MHz 1H NMR (CDCl3) δ 7.93 (1H, s), 7.36-7.17 (3H, m), 7.05 (1H, s), 6.94 (2H, d, J = 9.0 Hz), 6.48 (2H, d, J = 8.7 Hz), 5.49 (1H, br s), 5.45 (1H, d, J = 2.7 Hz), 3.96 (3H, s), 3.92 (3H, s), 3.71 (3H, s), 3.60 (3H, s), 2.55 (1H, br s); 75 MHz 13C NMR (CDCl3) δ 158.0, 155.2, 153.0, 152.7, 142.3, 140.6, 137.0, 131.7, 130.1, 127.1, 126.8, 125.0, 123.1, 121.9, 119.0, 113.4, 110.1, 105.8, 73.8, 61.8, 61.2, 56.3, 55.1, 49.8; HRMS m/z for C26H24O6 calcd 432.1573, found 432.1580; 300 MHz 1H NMR (acetone-d6) δ 8.29 (1H, s), 7.48 (1H, dd, J = 6.9, 1.5 Hz), 7.35 (1H, s), 7.27-7.15 (2H, m), 7.03 (2H, d, J = 9.0 Hz), 6.44 (2H, d, J = 9.0 Hz), 5.52 (1H, br s), 5.51 (1H, d, J = 4.5 Hz), 5.37 (1H, d, J = 4.5 Hz), 3.97 (3H, s), 3.87 (3H, s), 3.72 (3H, s), 3.55 (3H, s); 75 MHz 13C NMR (acetone-d6) δ 157.7, 155.0, 152.9, 152.8, 142.3, 141.4, 138.2, 132.9, 129.9, 127.5, 126.9, 124.5, 123.1, 122.1, 119.4, 112.6, 109.2, 106.8, 73.5, 61.1, 60.3, 55.7, 54.3, 49.3.

8,9,10-Trimethoxy-7-(4-methoxyphenyl)-7H-2-oxadibenzo[cd,h]azulen-6-one (18)

To a solution of 3 (9 mg, 0.0208 mmol) in CH2Cl2 (1 mL) was added Dess-Martin periodinane (11 mg, 0.025 mmol) at 0 °C. After being stirred at 0 °C for 10 min, the reaction mixture was diluted with Et2O. The mixture was filtered through Celite and rinsed with Et2O. The filtrate was evaporated in vacuo. The residue was purified by sgc (H:EA:CH2Cl2 = 3:1:1) to give 17 (9 mg, 100%). 300 MHz 1H NMR (CDCl3) δ 8.03 (1H, s), 7.79 (1H, d, J = 7.5 Hz), 7.52 (1H, d, J = 8.1 Hz), 7.33 (1H, t, J = 8.1 Hz), 7.03 (1H, s), 6.74 (2H, d, J = 9.0 Hz), 6.51 (2H, d, J = 8.7 Hz), 6.06 (1H, s), 3.98 (3H, s), 3.95 (3H, s), 3.85 (3H, s), 3.60 (3H, s); 75
MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 196.8, 158.1, 155.2, 153.7, 153.1, 143.0, 141.8, 131.2, 130.5, 128.1, 126.7, 125.2, 124.9, 123.7, 123.0, 121.7, 115.6, 113.8, 106.5, 62.2, 61.3, 56.8, 56.3, 55.2; HRMS m/z for C$_{26}$H$_{22}$O$_6$ calcd 430.1426, found 430.1424.

References


5. a) The elegant 3 + 2 strategy developed by Wender for the synthesis of indoles is a


10. In compound 3, the two-dimensional NOESY spectrum showed a strong interaction between the two methine hydrogens. The benzylic alcohol methine proton showed a NOE interaction only with the adjacent methine proton. If the stereochemistry was reversed, molecular models indicate that there would almost certainly be a strong NOE interaction with the hydrogen on C-5 of the benzofuran.
CHAPTER 2. DIRECT SYNTHESSES OF ISOFLAVANQUINONES

Introduction

Colutequinone A, colutequinone B, and claussequinone are members of a growing family of isoflavanquinones.

\[
\begin{align*}
R_1 &= R_2 = R_3 = R_4 = H: \text{ (1)} \\
R_1 &= \text{OMe}, R_2 = R_3 = R_4 = H: \text{ colutequinone A (3)} \\
R_1 &= R_2 = R_3 = \text{OMe}, R_4 = H: \text{ colutequinone B (4)} \\
R_1 &= \text{OH}, R_2 = R_4 = H, R_3 = \text{OMe: claussequinone (5)} \\
R_1 &= R_3 = \text{OMe}, R_2 = R_4 = H: \text{ O-methyl claussequinone (6)}
\end{align*}
\]

Colutequinones A\(^1\) and B\(^2\) were isolated from the root bark of *Colutea aborescens* and are known to have antimicrobial and antifungal activity. Claussequinone,\(^3\) which was isolated from the heartwood of *Dalbergia odorifera* (Leguminosae),\(^3c\) exhibits anti-inflammatory\(^4a\) and antifertility activity.\(^4b\) It also displays potent activity against bloodstream forms of *Trypanosoma cruzi* (Chagas' disease).\(^5\) Moreover, it is a feeding deterrent for the grass grub *Costelytra zealandica*.\(^6\) While no synthetic approaches to colutequinones A and B have been reported, claussequinone has been synthesized by Farkas and coworkers using thallium
trinitrate (TTN)-mediated rearrangement in the key step. As part of a program to develop environmentally benign radical reactions, we investigated a direct approach to isoflavonquinones.

Results and Discussion

As shown in the retrosynthetic analysis, we initially envisioned that these isoflavonquinones could be assembled via decarboxylative radical addition of carboxylic acids to benzoquinones. Carboxylic acids could be derived from 2-hydroxybenzaldehydes.

To explore the feasibility of this strategy, we first prepared carboxylic acids and substituted benzoquinones. Thus, chroman-3-carboxylic acid and 7-methoxychroman-3-carboxylic acid were prepared in 78 and 67% yields, respectively, by the procedure of Sato. Synthesis of 2,3-dimethoxybenzoquinone was achieved from 1,2,3-trimethoxybenzene using Matsumoto’s protocol. Silver oxide oxidation of 2-methoxyhydroquinone provided 2-methoxybenzoquinone in 99% yield.
In the literature, there aren’t many examples of radical additions to quinones. Barton et al. reported the reaction of acyl thiohydroxamates and benzoquinones under visible light.\textsuperscript{11}

Minisci and coworkers used persulfate and a catalytic amount of silver nitrate to generate radical from carboxylic acid or oxalic acid mono ester.\textsuperscript{12}

Similarly, Jacobsen added the phenoxyethyl radical to benzoquinone.\textsuperscript{13}

The mechanism of silver (I)-catalyzed persulfate reaction is shown below as proposed.
by Minisci.\textsuperscript{12a}

i) generation of the carbon-centered radical

$$S_2O_8^{2-} + 2 \text{Ag}^+ \rightarrow 2 \text{SO}_4^{2-} + 2 \text{Ag}^{2+}$$

$$\text{RCO}_2\text{H} + \text{Ag}^{2+} \rightarrow \text{CO}_2 + \text{H}^+ + \text{Ag}^+ + \text{R}^*$$

ii) addition to the quinone ring

iii) oxidation of the radical adduct in a redox chain

Before we applied persulfate-mediated radical chemistry to the synthesis of isoflavanquinones, we first conducted decarboxylative radical addition of cyclohexanecarboxylic acid to benzoquinone to find the optimal reaction conditions. Thus, a mixture of benzoquinone and cyclohexanecarboxylic acid was treated with a catalytic amount of silver nitrate and 1.5 equivalents of ammonium persulfate to give cyclohexyl benzoquinone 11 in good yield.

Encouraged by this result, we reacted chroman-3-carboxylic acid with benzoquinone
under the same condition. However, no reaction took place. The starting materials were just recovered with a small amount of decomposed product.

\[
\begin{align*}
\text{cat. AgNO}_3, (\text{NH}_4)_2\text{S}_2\text{O}_8 & \\
\text{CH}_3\text{CN/H}_2\text{O}, 70^\circ\text{C} & \\
\rightarrow & \\
\text{No reaction}
\end{align*}
\]

For comparison, we also carried out the reaction with commercially available 1,2,3,4-tetrahydro-2-naphthoic acid. Surprisingly, adduct 12 was obtained in a 55% unoptimized yield.

\[
\begin{align*}
\text{cat. AgNO}_3, (\text{NH}_4)_2\text{S}_2\text{O}_8 & \\
\text{CH}_3\text{CN/H}_2\text{O}, 70^\circ\text{C} & \\
\rightarrow & \\
55\% & \\
\text{12}
\end{align*}
\]

From the observation described above, we came to a tentative conclusion that a subtle electronic issue made a big difference although we were uncertain how the extra oxygen in 7 played a role in this reaction.

In the meantime, we found that hypervalent iodine reagents, such as iodosbenzene diacetate, could generate radicals from the corresponding carboxylic acid precursors.\(^{14}\)

Therefore, we used iodosbenzene diacetate as a radical generator. Gratifyingly, colutequinones A and B, as well as unnatural isoflavanquinones, were obtained albeit in low yield.

Modification of the reaction conditions by changing the ratio of reagents, temperatures, and solvents did not lead to any improvement in the chemical conversion of this process.
At this stage, we went back to the persulfate chemistry. We postulated that fast electron transfer might occur in relatively electron-rich 7 and 8 before radical addition, resulting in the cation species via loss of one electron.

Thus, we decided to introduce the electron-withdrawing group to carboxylic acids to avoid fast electron transfer.

In this regard, compounds 7 and 8 were nitrated. While 7 provided a 2:1 mixture of nitrated products 12a and 12b, 8 was nitrated at 6-position to give 13 as a single isomer.
With these compounds in hand, standard persulfate chemistry was undertaken. To our delight, 12a and 12b furnished radical adducts 14a and 14b as a mixture of regioisomers in 36% yield, although 13 still provided desired product 15 in low yield. We assumed that additional methoxy group in 13 still inhibited the reaction from occurring.

We also employed a stoichiometric amount of silver salt to prevent the possible deactivation of catalytic amount of silver(I) ion in the reaction medium. In this case, an 18% isolated yield of radical adduct 1 was observed along with coumarin 16. Compound 16 explained our rationale of electron transfer in the reaction mixture.
We next used compounds 12a and 12b as radical precursors and a stoichiometric amount of silver salt. This combination provided adducts 14a and 14b in 43% yield.

However, these compounds required further manipulation to be transformed into natural products. Therefore, we decided to pursue other routes to these natural products.

In an attempt to generate a vinylic radical from the precursor 17, we performed the reaction under the modified persulfate conditions. Similarly, carboxylic acid 18 was exposed to the same conditions. But these acids did not provide the desired adducts.
We've learned that electron-rich aromatic ring somehow prevents the radical addition from occurring. In this regard, we designed radical precursors in which two phenol groups were masked by electron withdrawing groups.

Compounds 19 and 20 were synthesized in a conventional manner from the commercially available 2,4-dihydroxybenzaldehyde. Thus, Wittig olefination, ester hydrolysis, bis O-acetylation, and catalytic hydrogenation provided the radical precursor 19 in good overall yield.

In a similar manner, 20 was prepared by bis O-triflation and hydrogenation of 21.

First, we undertook silver(I)-catalyzed persulfate reaction with 19. It gave a radical adduct 22 in 24-33% yield. Even if we increased the amount of the silver(I) salt to 1.1 equivalents, it did not improve the chemical yield.
For comparison, other precursors were tested.

<table>
<thead>
<tr>
<th>entry</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>product</th>
<th>yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OMe</td>
<td>H</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>H</td>
<td>23</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>OTf</td>
<td>OTf</td>
<td>24</td>
<td>8</td>
</tr>
</tbody>
</table>

Since triflates in the benzene ring decrease the electron density of the aromatic ring more than acetyloxy groups, we anticipated a better chemical yield. Rather, it gave a poorer result. In line with the effort to decrease the electron density, we also prepared 25 quantitatively from 7 by Birch reduction.$^{18}$

However, subjection of 25 to radical conditions described above gave only a 15% of
adduct 1. In the reaction mixture, we observed chroman-3-carboxylic acid 7, presumably as a consequence of the facile oxidation of 25 under the reaction condition.

![Chemical reaction diagram]

Concurrently, we designed a different approach toward these molecules. Phenyl radical would add preferably to 3-position of chromene or coumarin rather than to 4-position because of the formation of a more stable benzyl radical.

![Chemical structures]

Few radical addition to chromene or coumarin derivatives have been studied. For example, Russel and coworkers added \( t \)-butyl radical to coumarin in the presence of base.

![Radical addition reaction]

Thus, we employed several different radical or palladium reaction conditions to effect this strategy. Unfortunately, none of them afforded a desirable result. Only debrominated benzene was observed.
Chromene 27 was also prepared by the slight modification of the known procedure.\(^2\)

With 27 in hand, a palladium catalyzed Heck reaction\(^2\) was carried out. It failed to give the desired product.

At this point, we came up with a different strategy in which an intramolecular radical or Heck type process would lead to the desired transformation.
Toward this end, 2-iodophenol 28 and bromoketone 30 were prepared by known procedures.

Iodophenol 28 was alkylated with bromoketone 30 and potassium carbonate in boiling acetone in quantitative yield to give ketone 31. We reacted 31 with excess MeLi at -78 °C to
introduce the exo methylene group on the carbonyl group. To our surprise, instead of the tertiary alcohol as a result of the carbonyl attack, we obtained benzofuran 32 in very good yield. This observation led us to investigate the synthetic approach to the natural products possessing a benzofuran unit, which was discussed in the first part of this dissertation.

Treatment of 31 with Horner-Wadsworth-Emmons reagent afforded 33 as an E/Z mixture. Exposure of 33 to standard \( n\)-Bu\(_3\)SnH condition gave rise to 34 via a 5-exo radical attack in 85\% yield.\(^{24}\) We expected a 6-endo attack followed by the removal of CN radical,
but it did not happen. A similar approach was studied using a palladium-catalyzed intramolecular Heck reaction. They reported that five-membered ring formation was favored over six-membered ring formation despite the conditions in which a true hydride source was not added.

\[
\begin{align*}
\text{CO}_2\text{Me} & \\
Pd(OAc)_2, \text{PPh}_3 & \\
\text{Bu}_3\text{N}, \text{CH}_3\text{CN} & \\
\end{align*}
\]

Thus, we sought another approach. Boranes are useful radical precursors and might be good candidates for radical addition to benzoquinones.

There are literature precedents in which simple alkylboranes add to benzoquinones to give substituted benzoquinones after oxidation of the resulting hydroquinones.

To test this protocol, chromene 27 was reacted with BH₃ followed by the treatment of
benzoquinone and air. To our delight, this sequence provided the quinone 2 in 37% yield. Notably, the benzoquinone was obtained from the reaction mixture without need for a subsequent oxidation step.

For comparison, we employed a different borane reagent, catecholborane, for hydroboration. Renaud and coworkers reported radical addition to α,β-unsaturated carbonyl compounds using catecholborane. We adopt this method to effect our desired transformation.

The yield was a little lower than that of BH₃ case. Moreover, it was sometimes more difficult to isolate product from the reaction mixture because of the resulting catechol. Thus, we decided to use BH₃ for other transformations. We also used 2-chromene 37 to see if this gave a better result. 2-Chromene 37 was available in two steps from 35. However, it did not have an advantage over 3-chromene.
Three commercially available alkenes were examined with BH$_3$ and benzoquinone. While the first two alkenes gave good yields of the corresponding products, the third alkene provided only a trace amount of the product.

For some reason, large amount of unreacted chromene 27 was recovered after the reaction. We resubmitted the recovered chromene 27 to the same condition to increase the yield up to 65% yield. With this promising result in hand, our attention was next directed to
produce the appropriately substituted benzoquinone natural products in one step. Thus, we reacted the boranes with substituted benzoquinones.

To our surprise, no desired adducts were formed. The major product was the chromanol derived from oxidation of the borane with oxygen. This result was unexpected in light of a recent report on the successful regioselective addition of alkyl radicals to methoxybenzoquinone.\textsuperscript{27e} We also tested other functionalized benzoquinones for this reaction. No adducts were obtained, either.
Thus, we decided to manipulate the quinone 2 to add the required functionality onto the benzoquinone. To incorporate the dichloro\textsuperscript{31} or dihydroxy\textsuperscript{32} functionality onto the benzoquinone, we tried two procedures, but failed to get the desired products.

The regioselective addition of alcohols to benzoquinones has little precedent\textsuperscript{33}. Our
group recently published the regioselective addition of methanol to a phenanthrenequinone using a Lewis acid catalyst.\(^34\) Employing these conditions with 2 we obtained 40 in 70% yield. In 40, the proton at C-5 of the quinone (ortho to the methoxy group) has a chemical shift of 5.89 with a coupling constant of 2.4 Hz. The corresponding hydrogen in astragaluquinone\(^35\) has a coupling constant of 2.5 Hz.

The reaction of 2 with thiophenol and PTSA in methanol at 25 °C followed by oxidation with silver oxide produced adducts 41a and 41b in a 5:1 ratio in 93% combined yield. Although no precedent was found for the directed addition of thiophenol to substituted benzoquinones, the regiochemistry of thiophenol addition is in accord with our observation for the acid catalyzed addition of methanol to quinones. Oxidation of 41a with \(m\)CPBA\(^36\) in chloroform at 0 °C afforded a sulfoxide that was treated with methanol at reflux to afford \(O\)-methyl analog 6 of claussequinone in 70% yield. Its proton and carbon NMR were consistent with the structure of 6. Presumably, this transformation occurs by way of methanol addition to the activated benzoquinone followed by sulfoxide elimination. Compound 41b, the minor
product of thiol addition, was treated with sodium methoxide to afford compound 6 in 63% yield.

In summary, direct approaches to isoflavanquinones have been made utilizing three different radical generation methodologies - persulfate chemistry, hypervalent iodine chemistry, and borane chemistry. Synthetic scope and limitation of each strategy have been presented. Moreover, convenient procedures for the regiospecific addition of thiophenol and methanol to substituted benzoquinones have been developed during the study with boranes. These routes will be useful for the synthesis of quinone natural products with useful biological activity.

**Experimental Section**

Unless otherwise noted, materials were obtained from commercial suppliers and used
without purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane and benzene were distilled over calcium hydride. All experiments were performed under argon atmosphere unless otherwise noted. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or Bruker 400 MHz instrument. All chemical shifts are reported relative to CDCl₃ (7.26 ppm for ¹H and 77.06 ppm for ¹³C), unless otherwise noted. Coupling constants (J) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer and low resolution mass spectra were performed with a Finnegan 4023 mass spectrometer. Standard grade silica gel (60 Å, 32-63 μm) was used for a flash column chromatography.

Chroman-3-carboxylic acid (7)

To a solution of 2-hydroxybenzaldehyde (5.0 g, 40.943 mmol) and t-butyl acrylate (9.0 mL, 61.415 mmol) in DMF (82 mL) was added K₂CO₃ (5.66 g, 40.943 mmol) at rt. After being heated at 100 °C for 1 h, the mixture was heated at 135 °C for 14h. Then, additional t-butyl acrylate (9.0 mL, 61.415 mmol) was added to the reaction mixture. The mixture was heated at 135 °C for additional 24 h. After being cooled to rt, the mixture was diluted with ethyl acetate and acidified with 10% HCl. The organic layer was washed with H₂O three times and with brine one time, successively. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. t-Butyl ester was identified in the crude ¹H NMR. 300 MHz ¹H NMR (CDCl₃) δ 7.33 (1H, s), 7.22 (1H, t, J = 8.7 Hz), 7.13 (1H, d, J = 7.5 Hz), 6.91 (1H, t, J = 7.5 Hz), 6.83 (1H, d, J = 8.1 Hz), 4.95 (2H, s), 1.52 (9H, s).

The crude residue was diluted with trifluoroacetic acid (20 mL) and stirred at rt for 1 h. The solvent was evaporated under reduced pressure. To this residue was added large amount
of cold H$_2$O. The resulting precipitate was suction-filtered off and washed with H$_2$O several times. The solid was air-dried. The acid was identified in the crude $^1$H NMR. 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.57 (1H, s), 7.26 (1H, t, $J = 8.7$ Hz), 7.17 (1H, d, $J = 7.5$ Hz), 6.95 (1H, t, $J = 7.5$ Hz), 6.87 (1H, d, $J = 8.1$ Hz), 5.01 (2H, s).

The crude residue was dissolved in ethyl acetate and 10% Pd/C was added with care. After being stirred under H$_2$ balloon pressure for 6 h, the mixture was carefully filtered through Celite and washed with ethyl acetate. The filtrate was transferred to the separatory funnel. The organic layer was washed with saturated NaHCO$_3$ solution. The separated aqueous layer was then acidified with 10% HCl. The aqueous layer was extracted with ethyl acetate two times. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 5:1 to 2:1) to give 7 (5.684 g, 78%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.30-7.03 (2H, m), 7.03-6.70 (2H, m), 4.46 (1H, d, $J = 11.1$ Hz), 4.32-4.08 (1H, m), 3.30-2.82 (3H, m); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 179.1, 154.2, 130.0, 127.9, 121.2, 120.2, 117.0, 66.3, 38.6, 27.4, 16.6.

7-Methoxychroman-3-carboxylic acid (8)

The same procedure for 7 was applied.

$t$-Butyl ester: 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.30 (1H, d, $J = 0.6$ Hz), 7.03 (1H, d, $J = 8.4$ Hz), 6.47 (1H, dd, $J = 8.4$, 2.4 Hz), 6.39 (1H, d, $J = 2.4$ Hz), 4.92 (2H, d, $J = 1.2$ Hz), 3.85 (3H, s), 1.52 (9H, s).

Acid: 300 MHz $^1$H NMR (acetone-d$_6$) $\delta$ 7.45 (1H, s), 7.24 (1H, d, $J = 8.4$ Hz), 6.57 (1H, dd, $J = 8.4$, 2.4 Hz), 6.45 (1H, d, $J = 2.4$ Hz), 4.93 (2H, s).

8: 300 MHz $^1$H NMR (acetone-d$_6$) $\delta$ 6.99 (1H, d, $J = 8.4$ Hz), 6.45 (1H, dd, $J = 8.4$, 2.4 Hz), 6.32 (1H, d, $J = 2.4$ Hz), 4.38 (1H, dd, $J = 10.5$, 2.4 Hz), 4.12 (1H, dd, $J = 10.5$, 7.5 Hz), 3.72
(3H, s), 3.13-2.85 (3H, m); 75 MHz $^1$C NMR (acetone-d$_6$) $\delta$ 173.0, 159.5, 155.2, 130.4, 113.0, 107.6, 101.5, 66.7, 54.8, 38.2, 26.7.

**2,3-Dimethoxy-1,4-benzoquinone (9)**

To a solution of 1,2,3-trimethoxybenzene (5.0 g, 29.7 mmol) in AcOH (29.7 mL) were successively added K$_3$Fe(CN)$_6$ (1.2 g, 3.64 mmol) and H$_2$O$_2$ (30% solution, 7.4 mL, 65.34 mmol) at rt. After being stirred at rt for 1 h (exothermic reaction), the mixture was diluted with CH$_2$Cl$_2$ and washed with H$_2$O, saturated NaHCO$_3$ solution, and brine, successively. The organic layer was dried over MgSO$_4$, filtered, and concentrated in vacuo. The residue was purified by sgc (H:EA = 5:1) to give 9 (2.65 g, 53%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 6.60 (2H, s), 4.02 (6H, s).

**Methoxy-1,4-benzoquinone (10)**

To a solution of methoxyhydroquinone (500 mg, 3.568 mmol) in benzene (36 mL) were added Na$_2$SO$_4$ (1.06 g, 7.493 mmol) and Ag$_2$O (1.65 g, 7.136 mmol) at rt. The reaction flask was covered with aluminum foil and stirred overnight. The mixture was suction-filtered through Celite and washed with ethyl acetate. The filtrate was evaporated to give 10 (488 mg, 99%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 6.71 (2H, s), 5.95 (1H, s), 3.83 (3H, s).

**Cyclohexyl-1,4-benzoquinone (11)**

To a mixture of 1,4-benzoquinone (300 mg, 2.78 mmol) and cyclohexanecarboxylic acid (517 µL, 4.17 mmol) in CH$_3$CN (5 mL)/H$_2$O (5 mL) were added AgNO$_3$ (94 mg, 0.556 mmol) and (NH$_4$)$_2$S$_2$O$_8$ (698 mg, 3.058 mmol) at rt. After being heated at 70 °C for 6 h, the mixture was cooled to rt. The solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with H$_2$O and saturated NaHCO$_3$ solution, successively. The organic layer was dried over MgSO$_4$, filtered, and evaporated under reduced pressure. The
residue was purified by sgc (H:EA = 20:1) to give 11 (480 mg, 91%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 6.69 (1H, d, $J = 9.9$ Hz), 6.63 (1H, dd, $J = 9.9$, 2.4 Hz), 6.44 (1H, dd, $J = 2.1$, 0.9 Hz), 2.62 (1H, t, $J = 11.7$ Hz), 1.84-1.60 (5H, m), 1.45-1.24 (2H, m), 1.24-1.02 (3H, m); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 188.3, 187.2, 154.1, 137.2, 136.1, 130.9, 36.5, 32.2, 26.5, 26.1. 

(1,2,3,4-Tetrahydronaphthalen-2-yl)-1,4-benzoquinone (12)

The same procedure for 11 was applied. 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.20-7.02 (4H, m), 6.80 (1H, d, $J = 9.9$ Hz), 6.74 (1H, dd, $J = 9.9$, 2.1 Hz), 6.58 (1H, dd, $J = 2.4$, 1.2 Hz), 3.26-3.13 (1H, m), 3.07-2.84 (3H, m), 2.70 (1H, dd, $J = 15.9$, 11.1 Hz), 2.10-1.97 (1H, m), 1.82-1.65 (1H, m); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 188.1, 187.2, 153.0, 137.3, 136.3, 135.8, 135.3, 131.4, 129.2, 129.16, 126.3, 126.1, 35.1, 33.3, 29.1, 28.3; HRMS m/z for C$_{16}$H$_{14}$O$_2$ calcd 238.0994, found 238.0996.

(3,4-Dihydrobenzopyran-3-yl)-1,4-benzoquinone (1)

To a mixture of 1,4-benzoquinone (10 mg, 0.093 mmol) and 7 (49.7 mg, 0.279 mmol) in benzene (2 mL) was added PhI(OAc)$_2$ (30 mg, 0.093 mmol) at rt. After being heated to reflux overnight, the mixture was cooled to rt. The solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with saturated NaHCO$_3$ solution. The organic layer was dried over MgSO$_4$, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (H:EA = 5:1) to give 1 (6.0 mg, 27%, 92% based on the recovered 1,4-benzoquinone). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.13 (1H, t, $J = 7.5$ Hz), 7.07 (1H, d, $J = 7.5$ Hz), 6.89 (1H, t, $J = 7.5$ Hz), 6.83 (1H, d, $J = 7.5$ Hz), 6.82 (1H, dd, $J = 10.2$, 0.6 Hz), 6.74 (1H, ddd, $J = 9.9$, 2.4, 0.6 Hz), 6.56 (1H, dd, $J = 2.4$, 1.2 Hz), 4.29 (1H, ddd, $J = 10.5$, 3.0, 1.2 Hz), 4.08 (1H, ddd, $J = 10.8$, 6.6, 0.9 Hz), 3.54-3.42 (1H, m), 3.12 (1H, dd, $J = 16.5$, 5.7 Hz), 2.82 (1H, dd, $J = 16.2$, 6.9 Hz); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 187.5, 186.9, 154.2, 148.6,
137.1, 136.6, 133.0, 129.9, 128.1, 121.3, 120.2, 117.1, 68.3, 31.2, 29.7; HRMS m/z for C_{15}H_{12}O_{3} calcd 240.0786, found 240.0791.

(3,4-Dihydro-7-methoxybenzopyran-3-y1)-1,4-benzoquinone (2)

1) from the reaction of 8 and 1,4-benzoquinone using iodobenzene diacetate:

   The same procedure for 1 was applied.

2) from 27:

   To a solution of 7-methoxy-3-chromene 27 (800 mg, 4.94 mmol) in THF (4 mL) was added 1 M BH₃-THF (1.65 mL, 1.65 mmol) at 0 °C. After being stirred at rt for 5 h, H₂O (89 μL, 4.94 mmol) was added at 0 °C. Then benzoquinone (178 mg, 1.65 mmol) was added at rt in one portion. After being stirred at rt for 2 h, the mixture was evaporated in vacuo. The residue was purified by sgc (H:EA = 7:1) to give 2 (165 mg, 37%). 300 MHz ^1H NMR (CDCl₃) δ 6.95 (1H, d, J = 8.4 Hz), 6.81 (1H, d, J = 10.2 Hz), 6.73 (1H, dd, J = 10.2, 2.1 Hz), 6.55 (1H, dd, J = 2.1, 1.2 Hz), 6.49 (1H, dd, J = 8.4, 2.7 Hz), 6.38 (1H, d, J = 2.7 Hz), 4.27 (1H, dd, J = 10.8, 3.0 Hz), 4.07 (1H, dd, J = 10.8, 6.6 Hz), 3.76 (3H, s), 3.50-3.39 (1H, m), 3.06 (1H, dd, J = 15.9, 5.7 Hz), 2.75 (1H, dd, J = 15.9, 6.9 Hz); 75 MHz ^13C NMR (CDCl₃) δ 187.6, 186.9, 159.6, 154.9, 148.6, 137.1, 136.5, 133.0, 130.3, 112.2, 108.3, 101.8, 68.3, 55.6, 31.2, 29.0; HRMS m/z for C_{16}H_{14}O_{4} calcd 270.0892, found 270.0895; Mp 120-123 °C (lit. mp 125 °C); TLC (3:1 H:EA) Rf = 0.25.

2-(3,4-Dihydro-7-methoxybenzopyran-3-yl)-5,6-dimethoxy-1,4-benzoquinone (3)

   The same procedure for 1 was applied. 300 MHz ^1H NMR (CDCl₃) δ 6.94 (1H, d, J = 8.4 Hz), 6.48 (1H, dd, J = 8.7, 2.7 Hz), 6.37 (1H, d, J = 2.7 Hz), 6.37 (1H, s), 4.25 (1H, dd, J = 10.8, 3.0 Hz), 4.06 (1H, dd, J = 10.8, 6.0 Hz), 4.02 (3H, s), 4.01 (3H, s), 3.76 (3H, s), 3.50-3.40 (1H, m), 3.05 (1H, dd, J = 16.2, 6.0 Hz), 2.71 (1H, dd, J = 15.9, 6.3 Hz); 75 MHz ^13C
NMR \((\text{CDCl}_3)\) $\delta$ 184.3, 183.7, 159.6, 154.9, 146.8, 145.3, 144.9, 131.2, 130.3, 112.2, 108.3, 101.8, 68.4, 61.6, 61.5, 55.6, 31.0, 29.1; HRMS \(m/z\) for \(\text{C}_{18}\text{H}_{16}\text{O}_6\) calcd 330.1103, found 330.1109.

2-(3,4-Dihydro-7-methoxybenzopyran-3-yl)-3,5-dimethoxy-1,4-benzoquinone (4)

The same procedure for 1 was applied. 300 MHz $^1H$ NMR \((\text{CDCl}_3)\) $\delta$ 6.92 (1H, d, $J = 8.4$ Hz), 6.47 (1H, dd, $J = 8.1, 2.4$ Hz), 6.41 (1H, d, $J = 2.7$ Hz), 5.86 (1H, s), 4.44 (1H, dd, $J = 10.8, 10.2$ Hz), 4.13 (1H, ddd, $J = 10.2, 3.3, 3.0$ Hz), 3.97 (3H, s), 3.81 (3H, s), 3.77 (3H, s), 3.70-3.55 (1H, m), 3.13 (1H, dd, $J = 15.0, 12.0$ Hz), 2.66 (1H, ddd, $J = 15.0, 5.1, 2.1$ Hz); 75 MHz $^{13}C$ NMR \((\text{CDCl}_3)\) $\delta$ 186.9, 178.4, 159.3, 157.4, 155.9, 155.3, 131.6, 130.2, 114.1, 107.7, 107.6, 101.8, 67.9, 61.6, 56.7, 55.6, 31.4, 29.4; HRMS \(m/z\) for \(\text{C}_{18}\text{H}_{16}\text{O}_6\) calcd 330.1103, found 330.1109.

2-(3,4-Dihydro-7-methoxybenzopyran-3-yl)-5-methoxy-1,4-benzoquinone (6)

1) from the reaction of 8 and 10 using iodobenzene diacetate:

The same procedure for 1 was applied.

2) from 42:

The sulfoxide 42 (35 mg, 0.089 mmol) was dissolved in MeOH (3 mL). The solution was heated to reflux overnight. The solvent was evaporated and the residue was purified by sgc (H:EA = 3:1) to afford 6 (18.7 mg, 70%). 300 MHz $^1H$ NMR \((\text{CDCl}_3)\) $\delta$ 6.95 (1H, d, $J = 8.4$ Hz), 6.48 (1H, dd, $J = 8.4, 2.4$ Hz), 6.48 (1H, d, $J = 1.2$ Hz), 6.37 (1H, d, $J = 2.7$ Hz), 5.97 (1H, s), 4.26 (1H, ddd, $J = 11.1, 3.3, 1.2$ Hz), 4.07 (1H, ddd, $J = 10.8, 6.0, 1.2$ Hz), 3.82 (3H, s), 3.76 (3H, s), 3.53-3.42 (1H, m), 3.06 (1H, dd, $J = 16.5, 6.3$ Hz), 2.73 (1H, dd, $J = 15.9, 6.3$ Hz); 75 MHz $^{13}C$ NMR \((\text{CDCl}_3)\) $\delta$ 186.9, 182.3, 159.6, 158.7, 154.9, 149.5, 131.1, 130.3, 112.3, 108.3, 108.1, 101.8, 68.5, 56.5, 55.5, 31.1, 29.1; HRMS \(m/z\) for \(\text{C}_{17}\text{H}_{16}\text{O}_5\) calcd
300.0998, found 300.1002; TLC (2:1 H:EA) $R_f = 0.36$.

8-Nitrochroman-3-carboxylic acid (12a) and 5-Nitrochroman-3-carboxylic acid (12b)

To a solution of 7 (256 mg, 1.44 mmol) and Ac$_2$O (768 µL) in CH$_2$Cl$_2$ (2 mL) were added HNO$_3$ (64 µL, 1.44 mmol) and AcOH (172 µL) at 0 °C. After being stirred at rt overnight, the solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with H$_2$O. The organic layer was dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was diluted with toluene and evaporated in vacuo to give 12a/b (321 mg, 100%) as a 2:1 mixture. 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 8.10-6.85 (3H, m), 4.67-4.25 (2H, m), 3.30-3.05 (3H, m).

7-Methoxy-6-nitrochroman-3-carboxylic acid (13)

The same procedure for 12a/b was applied. 300 MHz $^1$H NMR (acetone-d$_6$) $\delta$ 7.77 (1H, s), 6.57 (1H, s), 4.48 (1H, dd, $J = 10.5, 2.7$ Hz), 4.32 (1H, dd, $J = 10.8, 7.5$ Hz), 3.89 (3H, s), 3.25-2.95(3H, m).

(3,4-Dihydro-8-nitrobenzopyran-3-yl)-1,4-benzoquinone (14a) and (3,4-Dihydro-6-nitrobenzopyran-3-yl)-1,4-benzoquinone (14b)

The same procedure for 11 was applied.

14a: 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.73 (1H, d, $J = 7.8$ Hz), 7.31 (1H, d, $J = 7.8$ Hz), 6.96 (1H, t, $J = 7.8$ Hz), 6.84 (1H, d, $J = 9.9$ Hz), 6.77 (1H, dd, $J = 9.9, 2.4$ Hz), 6.53 (1H, dd, $J = 2.4, 1.2$ Hz), 4.48 (1H, dd, $J = 11.1, 3.3$ Hz), 4.21 (1H, dd, $J = 11.7, 7.8$ Hz), 3.58-3.47 (1H, m), 3.17 (1H, dd, $J = 16.2, 5.7$ Hz), 2.91 (1H, dd, $J = 17.1, 8.4$ Hz).

14b: 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 8.10-8.00 (2H, m), 6.92 (1H, d, $J = 9.9$ Hz), 6.94 (1H, d, $J = 10.2$ Hz), 6.77 (1H, dd, $J = 10.2, 2.4$ Hz), 6.53 (1H, d, $J = 2.4$ Hz), 4.41 (1H, dd, $J = 11.1, 3.3$ Hz), 4.19 (1H, dd, $J = 10.8, 6.9$ Hz), 3.55-3.45 (1H, m), 3.15 (1H, dd, $J = 16.2, 5.4$ Hz),
2.91 (1H, dd, J = 16.8, 7.8 Hz).

(3,4-Dihydro-7-methoxy-6-nitrobenzopyran-3-yl)-1,4-benzoquinone (15)

The same procedure for 11 was applied. 300 MHz $^1$H NMR (CDCl$_3$) δ 7.83 (1H, s), 6.84 (1H, d, J = 9.6 Hz), 6.77 (1H, dd, J = 9.9, 2.4 Hz), 6.55 (1H, dd, J = 2.4, 1.2 Hz), 6.50 (1H, s), 4.38 (1H, dd, J = 10.8, 2.1 Hz), 4.16 (1H, dd, J = 12.0, 6.9 Hz), 3.92 (3H, s), 3.54-3.40 (1H, m), 3.07(1H, dd, J = 16.2, 5.7 Hz), 2.81(1H, dd, J = 15.9, 7.2 Hz).

2-Oxo-2$\beta$-chromene-3-carboxylic acid (17)

To a mixture of 2-hydroxybenzaldehyde (2.44 g, 20 mmol) and malonic acid (3.12 g, 30 mmol) in H$_2$O (6.6 mL) was added Montmorillonite KSF (2 g) at rt. After being heated to reflux overnight, the mixture was cooled down to rt. The solid was suction-filtered off and rinsed with H$_2$O. The solid was suspended in MeOH (120 mL) and heated for 5 min. The suspension was filtered through Celite and washed with MeOH. The filtrate was evaporated in vacuo to give 17. 300 MHz $^1$H NMR (acetone-d$_6$) δ 8.97 (1H, s), 8.04 (1H, dd, J = 8.1, 1.8 Hz), 7.87 (1H, t, J = 7.5 Hz), 7.62-7.50 (2H, m).

2-Oxochroman-3-carboxylic acid (18)

17 (350 mg, 1.842 mmol) was dissolved in ethyl acetate and 10% Pd/C (50 mg) was added with care. After being stirred under H$_2$ balloon pressure for 8 h, the mixture was carefully filtered through Celite and washed with ethyl acetate. A mixture of 18 and decarboxylated product was identified in the crude $^1$H NMR. The filtrate was transferred to the separatory funnel. The organic layer was washed with saturated NaHCO$_3$ solution. The separated aqueous layer was then acidified with 10% HCl. The aqueous layer was extracted with ethyl acetate two times. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo to give pure 18. 300 MHz $^1$H NMR (acetone-d$_6$) δ 7.40-7.28 (2H, m),
7.15 (1H, t, J = 7.5 Hz), 7.05 (1H, d, J = 7.8 Hz), 3.97 (1H, t, J = 6.9 Hz), 3.37 (2H, d, J =
6.6 Hz), 2.84 (1H, br s).

3-(2,4-Dihydroxyphenyl)acrylic acid (21)

To a suspension of 2,4-dihydroxybenzaldehyde (5.92 g, 42.86 mmol) in benzene (150
mL) was added (carbethoxymethylene)triphenylphosphorane (19.42 g, 55.74 mmol) at rt.
After being stirred at rt overnight, the mixture was concentrated in vacuo. The residue was
purified by sgc (H:EA = 2:1 to 1:1) to give α,β-unsaturated ester (8.469 g, 95%). 300 MHz
$^1$H NMR (acetone-$d_6$) δ 8.93 (2H, br s), 7.92 (1H, d, J = 16.2 Hz), 7.44 (1H, d, J = 8.7 Hz),
6.52-6.37 (3H, m), 4.17 (2H, q, J = 7.2 Hz), 1.26 (3H, t, J = 7.2 Hz); 75 MHz $^{13}$C NMR
(acetone-$d_6$) δ 168.2, 161.0, 158.5, 140.7, 130.8, 114.4, 114.0, 108.5, 103.0, 60.1, 14.1.

The ester (12.875 g, 61.9 mmol) was dissolved in a solution of NaOH (8.67 g, 216.7
mmol) in H$_2$O (150 mL) at rt. After being heated to reflux for 1 h, the mixture was cooled to
rt. The mixture was acidified with c-HCl at 0 °C and extracted with ethyl acetate two times.
The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo to afford acid 21
(11.14 g, 100%). 300 MHz $^1$H NMR (acetone-$d_6$) δ 9.05 (2H, br s), 7.94 (1H, d, J = 16.2 Hz),
7.46 (1H, d, J = 8.7 Hz), 6.52-6.37 (3H, m).

3-(2,4-Diacetoxyphenyl)propionic acid (19)

To a solution of acid 21 (1.71 g, 9.52 mmol) in THF (78 mL) were successively added
Ac$_2$O (1.98 mL, 20.94 mmol), triethylamine (4.1 mL, 29.51 mmol), and DMAP (116 mg,
0.95 mmol) at 0 °C. After being stirred at rt for 5h, the mixture was concentrated in vacuo.
The residue was acidified with 10% HCl and extracted with ethyl acetate two times. The
organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo to give diacetates (2.5
g, 100%). 300 MHz $^1$H NMR (acetone-$d_6$) δ 7.88 (1H, d, J = 8.4 Hz), 7.70 (1H, d, J = 15.9
Hz), 7.12 (1H, dd, J = 8.7, 2.4 Hz), 7.07 (1H, d, J = 2.4 Hz), 6.54 (1H, d, J = 16.2 Hz), 2.37 (3H, s), 2.26 (3H, s).

Diacetates (1 g, 3.79 mmol) was dissolved in ethyl acetate and 10% Pd/C (100 mg) was added with care. After being stirred under H₂ balloon pressure for 8 h, the mixture was carefully filtered through Celite and washed with ethyl acetate. The filtrate was evaporated to give 19 (1g, 100%). 300 MHz ¹H NMR (acetone-d₆) δ 7.37 (1H, d, J = 8.1 Hz), 6.98 (1H, dd, J = 8.1, 2.4 Hz), 6.92 (1H, d, J = 2.4 Hz), 2.83 (2H, t, J = 7.2 Hz), 2.58 (2H, t, J = 7.8 Hz), 2.31 (3H, s), 2.24 (3H, s); 75 MHz ¹³C NMR (acetone-d₆) δ 173.2, 168.9, 168.8, 150.0, 149.6, 130.6, 130.5, 119.5, 116.6, 33.7, 24.9, 20.3, 20.1.

3-(2,4-Bis-trifluoromethanesulfonyloxyphenyl)propionic acid (20)

To a solution of acid 21 (530 mg, 2.94 mmol) in THF (10 mL) was added 60% NaH (471 mg, 11.76 mmol) at 0 °C. After 5 min, PhN(Tf₂)₂ (3.26 g, 9.11 mmol) was added at 0 °C in one portion. After being stirred at rt overnight, the mixture was concentrated in vacuo. The residue was diluted with ethyl acetate and washed with 10% HCl. The organic layer was dried over MgSO₄, filtered, and evaporated under reduced pressure. The residue was purified by sgc (H:EA = 2:1 to 1:1 then, CH₂Cl₂:MeOH = 10:1) to give bis-triflates (822 mg, 63%). 300 MHz ¹H NMR (acetone-d₆) δ 8.28 (1H, d, J = 8.7 Hz), 7.85 (1H, d, J = 11.1 Hz), 7.83 (1H, d, J = 2.4 Hz), 7.75 (1H, dd, J = 9.0, 2.4 Hz), 6.79 (1H, d, J = 15.9 Hz).

Bis-triflates (822 mg, 1.85 mmol) was dissolved in ethyl acetate and 10% Pd/C (80 mg) was added with care. After being stirred under H₂ balloon pressure for 5 h, the mixture was carefully filtered through Celite and washed with ethyl acetate. The filtrate was evaporated to give 20 (825 mg, 100%). 300 MHz ¹H NMR (acetone-d₆) δ 7.83 (1H, d, J = 8.1 Hz), 7.71-7.53 (2H, m), 3.11 (2H, t, J = 7.2 Hz), 2.77 (2H, t, J = 7.3 Hz).
2-(2,4-Diacetoxyphenyl)ethyl-1,4-benzoquinone (22)

The same procedure for 11 was applied. 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.22 (1H, d, $J =$ 8.4 Hz), 6.95 (1H, dd, $J =$ 8.4, 2.4 Hz), 6.87 (1H, d, $J =$ 2.4 Hz), 6.76 (1H, d, $J =$ 9.9 Hz), 6.71 (1H, dd, $J =$ 10.2, 2.1 Hz), 6.51-6.46 (1H, m), 2.80-2.60 (4H, m), 2.35 (3H, s), 2.27 (3H, s); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 187.7, 187.5, 169.3, 169.25, 149.8, 149.3, 148.2, 137.0, 136.7, 133.4, 130.6, 129.9, 119.6, 116.5, 30.6, 29.0, 21.3, 21.1; HRMS m/z for C$_{18}$H$_{16}$O$_6$ calcd 328.0947, found 328.0954.

2-Phenethyl-1,4-benzoquinone (23)

The same procedure for 11 was applied. 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.34-7.13 (5H, m), 6.77 (1H, d, $J =$ 9.9 Hz), 6.70 (1H, dd, $J =$ 9.9, 2.1 Hz), 6.52-6.47 (1H, m), 2.90-2.80 (2H, m), 2.80-2.70 (2H, m); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 187.9, 187.6, 148.6, 140.5, 137.0, 136.6, 133.2, 128.8, 128.6, 126.6, 34.2, 31.2.

2-(2,4-Bis-trifluoromethanesulfonyloxyphenyl)ethyl-1,4-benzoquinone (24)

The same procedure for 11 was applied. 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.40-7.12 (3H, m), 6.76 (1H, d, $J =$ 10.2 Hz), 6.70 (1H, dd, $J =$ 9.9, 2.4 Hz), 6.52-6.48 (1H, m), 2.90-2.78 (2H, m), 2.78-2.68 (2H, m).

5,8-Dihydrochroman-3-carboxylic acid (25)

To a solution of 7 (53 mg, 0.298 mmol) in EtOH (0.696 mL, 11.92 mmol) was added gaseous NH$_3$ at -78 °C. Then, small pieces of Li metal (40 mg, 5.96 mmol) was added to this mixture at -78 °C. After being stirred at -50 °C for 10 min (dark blue color disappeared), the excess NH$_3$ was blown out using argon. The residue was diluted with cold H$_2$O. To this mixture was added one drop of bromocresol blue (indicator) at 0 °C. Then, 10% HCl was dropwise added to the reaction mixture at 0 °C (up to pH 4 or 5). The mixture was extracted
with ethyl acetate two times. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo to give 25 (54 mg, 100%). 300 MHz \(^1\)H NMR (CDCl₃) δ 5.65 (2H, br s), 4.23 (1H, ddd, \(J = 10.5, 3.6, 1.5\) Hz), 3.98 (1H, d, \(J = 10.5, 8.7\) Hz), 3.05-2.90 (1H, m), 2.83-2.51 (4H, m), 2.27 (1H, dd, \(J = 16.5, 8.7\) Hz), 2.11 (1H, dd, \(J = 16.8, 6.3\) Hz); 75 MHz \(^13\)C NMR (CDCl₃) δ 179.3, 144.8, 124.4, 123.6, 101.1, 65.7, 39.2, 31.3, 28.3, 27.2.

3-(3-Methoxyphenoxy)propanal diethyl acetal (26)

To a solution of NaOH (3.6 g, 93.1 mmol) in H₂O (10 mL) was added 3-methoxyphenol (8 mL, 67.3 mmol) at rt. After being stirred at rt for 30 min, 3-chloropropionaldehyde diethyl acetal (6.0 mL, 35.8 mmol) was slowly added to the mixture at rt. After being heated to reflux overnight, the mixture was cooled down to rt. The mixture was diluted with Et₂O and washed with 15% NaOH and brine, successively. The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give 26 (8.644 g, 95%). 400 MHz \(^1\)H NMR (CDCl₃) δ 7.15 (1H, t, \(J = 8.0\) Hz), 6.53-6.40 (3H, m), 4.73 (1H, t, \(J = 5.6\) Hz), 4.02 (2H, t, \(J = 6.4\) Hz), 3.77 (3H, s), 3.57-3.45 (2H, m), 2.07 (2H, q, \(J = 6.4\) Hz), 1.19 (6H, t, \(J = 7.2\) Hz).

7-Methoxy-2H-chromene (27)

To a solution of the acetal 26 (9.6766 g, 38.1 mmol) in THF (72 mL) was added 15% HCl (54 mL) at rt. After being heated at 85 °C for 30 min, the organic solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with H₂O, saturated NaHCO₃ solution, and brine, successively. The organic layer was dried over MgSO₄, filtered, and evaporated under reduced pressure. The residue was purified by sgc (H:EA = 20:1) to afford 27 (4.0226 g, 65%). 300 MHz \(^1\)H NMR (CDCl₃) δ 6.89 (1H, d, \(J = 8.1\) Hz), 6.50-6.35 (3H, m), 5.63 (1H, td, \(J = 9.6, 3.6\) Hz), 4.80 (2H, dd, \(J = 3.6, 1.8\) Hz), 3.77 (3H, s); 75 MHz
$^{13}$C NMR (CDCl$_3$) $\delta$ 160.9, 155.6, 127.5, 124.5, 119.1, 116.0, 107.1, 102.0, 65.9, 55.5.

2-Iodo-5-methoxyphenol (28)

To a suspension of 3-methoxyphenol (5 g, 40.28 mmol) and AgCF$_3$CO$_2$ (8.9 g, 40.28 mmol) in CHCl$_3$ (40 mL) was dropwise added a solution of I$_2$ (10.22 g, 40.28 mmol) in CHCl$_3$ (322 mL) at rt. After the addition was complete, the mixture was stirred at rt overnight. The mixture was filtered through Celite and washed with CHCl$_3$. The filtrate was washed with saturated Na$_2$S$_2$O$_3$ solution and saturated NaHCO$_3$ solution, successively. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (CH$_2$Cl$_2$ only) to give 28 (7.179 g, 71%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.48 (1H, d, $J$ = 8.7 Hz), 6.59 (1H, d, $J$ = 2.7 Hz), 6.33 (1H, dd, $J$ = 8.7, 2.7 Hz), 5.41 (1H, br s), 3.77 (3H, s); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 161.9, 155.9, 138.3, 109.6, 101.2, 74.7, 55.7.

2',4',5'-Trimethoxyacetophenone (29)

A mixture of 1,2,4-trimethoxybenzene (5 g, 29.73 mmol) and I$_2$ (59.5 mg) in Ac$_2$O (28 mL, 29.73 mmol) was heated to reflux overnight. After being cooled down to rt, the mixture was concentrated in vacuo. The residue was diluted with ethyl acetate and washed with saturated NaHCO$_3$ solution and saturated Na$_2$S$_2$O$_3$ solution, successively. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (residue was loaded with benzene and eluted with H:EA = 1:1) to give 29 (4.374 g, 70%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.43 (1H, s), 6.50 (1H, s), 3.95 (3H, s), 3.92 (3H, s), 3.87 (3H, s).

2-Bromo-1-(2,4,5-trimethoxyphenyl)ethanone (30)

To a solution of 29 (5.3967 g, 25.68 mmol) in ethyl acetate (43 mL) and CHCl$_3$ (43 mL) was added CuBr$_2$ (11.47 g, 51.36 mmol) at rt. After being heated at 85 °C for 10 h, the
mixture was cooled to rt. The mixture was filtered through Celite and washed with CH₂Cl₂. The filtrate was concentrated in vacuo. The residue was suspended in solvent (H:EA = 2:1), filtered, and rinsed with small amount of solvent (H:EA = 2:1). The solid 30 (4.1 g) was dried under reduced pressure. The filtrate was concentrated and the resulting residue was purified by sgc (H:EA = 3:1 to 1:1) to give 30 (1.464 g, total yield: 75%). 300 MHz ^1H NMR (CDCl₃) δ 7.47 (1H, s), 6.50 (1H, s), 4.59 (2H, s), 3.97 (3H, s), 3.96 (3H, s), 3.88 (3H, s).

2-(2-Iodo-5-methoxyphenoxy)-l-(2,4,5-trimethoxyphenyl)ethanone (31)

To a mixture of 28 (3.8 g, 15.23 mmol) and 30 (4.4 g, 15.23 mmol) in acetone (84 mL) was added K₂CO₃ (2.1 g, 15.23 mmol) at rt. After being heated to reflux for 5 h, the mixture was concentrated in vacuo. The residue was diluted in CH₂Cl₂ and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue (6.974 g, 100%) was pure enough to carry out the next reaction. For NMR data, the residue was suspended in solvent (H:EA = 2:1), filtered, and rinsed with small amount of solvent (H:EA = 2:1) to give pure 31. 300 MHz ^1H NMR (CDCl₃) δ 7.65 (1H, d, J = 8.7 Hz), 7.54 (1H, s), 6.51 (1H, s), 6.33 (1H, dd, J = 8.4, 2.4 Hz), 6.26 (1H, d, J = 2.7 Hz), 5.26 (2H, s), 3.98 (3H, s), 3.96 (3H, s), 3.87 (3H, s), 3.74 (3H, s).

6-Methoxy-3-(2,4,5-trimethoxyphenyl)benzofuran (32)

To a solution of MeLi (1.4 M solution in THF, 337 µL, 0.471 mmol) in THF (2 mL) was dropwise added a solution of ketone 31 (72 mg, 0.157 mmol) in THF (4 mL + 1 mL for rinse) at −78 °C via cannula. After being stirred at −78 °C for 5 min, the mixture was quenched with saturated NH₄Cl at −78 °C. The mixture was concentrated in vacuo. The residue was diluted with CH₂Cl₂, washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated to dryness. The resulting residue was purified by sgc (H:EA = 2:1) to give
benzofuran 32 (45 mg, 91%). 300 MHz $^1$NMR (CDCl$_3$) $\delta$ 7.82 (1H, s), 7.58 (1H, d, $J$ = 8.7 Hz), 7.26 (1H, s), 7.06 (1H, d, $J$ = 2.1 Hz), 6.92 (1H, dd, $J$ = 8.7, 2.4 Hz), 6.68 (1H, s), 3.96 (3H, s), 3.91 (3H, s), 3.87 (3H, s), 3.83 (3H, s); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 158.1, 156.4, 151.6, 149.2, 143.4, 142.6, 121.3, 120.9, 117.5, 114.0, 112.8, 112.0, 98.6, 96.3, 57.0, 56.7, 56.4, 56.0; HRMS m/z for C$_{18}$H$_{18}$O$_5$ calcd 314.1154, found 314.1160.

4-(2-Iodo-5-methoxyphenoxy)-3-(2,4,5-trimethoxyphenyl)but-2-enenitrile (33)

To a suspension of 60% NaH (196 mg, 4.91 mmol) in THF (10 mL) was dropwise added diethyl (cyanomethyl)phosphonate (882 µL, 5.45 mmol) at 0 °C. After being stirred at rt for 20 min, a solution of 31 (500 mg, 1.09 mmol) in THF (22 mL + 10 mL for rinse) was transferred to the mixture at 0 °C via cannula. After being stirred at rt for 30 min, the mixture was quenched with saturated NH$_4$Cl at 0 °C. The organic solvent was evaporated in vacuo. The residue was diluted with CH$_2$Cl$_2$ and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 3:1 to 2:1) to give 33 (480 mg, 91%) as a cis/trans mixture. Two isomers were separated by sgc for NMR data although we did not determine which one is which. Ratio of upper spot to lower spot = 1.4:1

Upper spot: 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.52 (1H, d, $J$ = 8.7 Hz), 6.76 (1H, s), 6.51 (1H, d, $J$ = 2.7 Hz), 6.51 (1H, s), 6.32 (1H, dd, $J$ = 8.7, 2.7 Hz), 5.78 (1H, s), 5.29 (2H, s), 3.91 (3H, s), 3.81 (3H, s), 3.80 (3H, s), 3.77 (3H, s).

Lower spot: 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.65 (1H, d, $J$ = 8.7 Hz), 6.86 (1H, s), 6.46 (1H, s), 6.45 (1H, d, $J$ = 2.7 Hz), 6.37 (1H, dd, $J$ = 8.4, 2.4 Hz), 6.07 (1H, t, $J$ = 1.8 Hz), 4.91 (2H, d, $J$ = 2.1 Hz), 3.94 (3H, s), 3.88 (3H, s), 3.86 (3H, s), 3.78 (3H, s).

[6-Methoxy-3-(2,4,5-trimethoxyphenyl)-2,3-dihydrobenzofuran-3-yl]acetonitrile (34)
To a solution of 33 (80 mg, 0.166 mmol) in benzene (8.3 mL) were added \( n-\text{Bu}_3\text{SnH} \) (89 \( \mu\text{L}, 0.332 \text{ mmol} \)) and AIBN (5.5 mg, 0.033 mmol) at rt. After being heated at 87 °C overnight, the mixture was concentrated in vacuo. The residue was purified by sgc (H:EA = 3:1 to 1:1) to give 34 (50 mg, 85%). 300 MHz \( ^1\text{H NMR} \) (CDCl\textsubscript{3}) \( \delta \) 7.46 (1H, d, \( J = 8.4 \) Hz), 6.79 (1H, s), 6.59 (1H, dd, \( J = 8.4, 2.4 \) Hz), 6.56 (1H, s), 6.45 (1H, d, \( J = 2.1 \) Hz), 4.74 (1H, d, \( J = 9.9 \) Hz), 4.61 (1H, d, \( J = 9.9 \) Hz), 3.88 (3H, s), 3.87 (3H, s), 3.80 (3H, s), 3.68 (3H, s), 3.32 (1H, d, \( J = 16.5 \) Hz), 3.06 (1H, d, \( J = 16.5 \) Hz).

**7-Methoxychroman-2-one (35)**

7-Methoxycoumarin (10.8 g, 66.61 mmol) was dissolved in ethyl acetate and 10% Pd/C (1 g) was added with care. After being stirred under \( \text{H}_2 \) balloon pressure for 7 h, the mixture was carefully filtered through Celite and washed with ethyl acetate. The filtrate was evaporated to give 35 (11.87 g, 100%). 400 MHz \( ^1\text{H NMR} \) (CDCl\textsubscript{3}) \( \delta \) 7.05 (1H, d, \( J = 8.0 \) Hz), 6.63 (1H, dd, \( J = 8.4, 2.4 \) Hz), 6.58 (1H, d, \( J = 2.0 \) Hz), 3.77 (3H, s), 2.91 (2H, t, \( J = 6.8 \) Hz), 2.74 (2H, t, \( J = 6.4 \) Hz).

**7-Methoxychroman-2-ol (36)**

To a solution of 35 (2.4367 g, 13.68 mmol) in \( \text{CH}_2\text{Cl}_2 \) was dropwise added DIBAL (1 M solution in THF, 20.3 mL, 20.3 mmol) at \(-78 \) °C. After being stirred at \(-78 \) °C for 20 min, the mixture was quenched with saturated \( \text{NH}_4\text{Cl} \) with care. After being stirred at rt for 1 h, the mixture was suction-filtered through Celite and rinsed with \( \text{CH}_2\text{Cl}_2 \). The filtrate was evaporated in vacuo. The residue was purified by sgc (H:EA = 4:1) to give 36 (1.478 g, 60%). 300 MHz \( ^1\text{H NMR} \) (CDCl\textsubscript{3}) \( \delta \) 6.95 (1H, d, \( J = 8.4 \) Hz), 6.48 (1H, dd, \( J = 8.4, 2.4 \) Hz), 6.41 (1H, d, \( J = 2.4 \) Hz), 5.55 (1H, t, \( J = 2.7 \) Hz), 3.73 (3H, s), 2.98-2.82 (1H, m), 2.63 (1H, td, \( J = 16.2, 5.4 \) Hz), 2.05-1.85 (2H, m); 75 MHz \( ^{13}\text{C NMR} \) (CDCl\textsubscript{3}) \( \delta \) 159.3, 153.1, 130.0, 114.5,
7-Methoxy-4H-chromene (37)

A mixture of 36 (4 g, 22.2 mmol) and anhydrous CuSO₄ (570 mg, 3.55 mmol) was heated at 150 °C under 10 or 20 mmHg. After 2 h, the mixture was filtered through Celite and washed with ethyl acetate. The filtrate was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give a small amount of 37. 300 MHz ¹H NMR (CDCl₃) δ 6.91 (1H, d, J = 8.7 Hz), 6.58 (1H, dd, J = 8.4, 2.7 Hz), 6.47 (1H, dt, J = 6.3, 2.1 Hz), 6.43 (1H, d, J = 2.4 Hz), 4.95 (1H, dt, J = 6.3, 3.6 Hz), 3.78 (3H, s), 3.37-3.30 (2H, m); 75 MHz ¹³C NMR (CDCl₃) δ 159.2, 152.3, 140.6, 130.1, 112.1, 110.0, 101.8, 101.1, 55.6, 22.6.

Tetrahydropyran-3-yl-1,4-benzoquinone (38)

The same procedure for 2 from 27 was applied. 300 MHz ¹H NMR (CDCl₃) δ 6.76 (1H, d, J = 9.9 Hz), 6.71 (1H, dd, J = 10.2, 2.4 Hz), 6.61 (1H, dd, J = 2.1, 0.9 Hz), 3.99-3.84 (2H, m), 3.55-3.39 (1H, m), 3.30 (1H, dd, J = 11.1, 9.3 Hz), 3.10-2.95 (1H, m), 1.99-1.84 (1H, m), 1.83-1.61 (2H, m), 1.61-1.43 (1H, m); 75 MHz ¹³C NMR (CDCl₃) δ 187.8, 186.7, 149.7, 137.2, 136.3, 132.7, 71.7, 68.5, 35.1, 28.4, 25.2; HRMS m/z for C₁₁H₁₂O₃ calcd 192.0786, found 192.0789.

(6-Methoxytetrahydropyran-3-yl)-1,4-benzoquinone (39)

The same procedure for 2 from 27 was applied. 300 MHz ¹H NMR (CDCl₃) δ 6.73-6.40 (3H, m), 4.55 and 4.33 (1H, dd, J = 5.7, 3.0 Hz), 3.92 (1H, dd, J = 11.4, 3.6 Hz), 3.34 (1H, dd, J = 11.4, 6.9 Hz), 3.29 and 3.21 (3H, s), 2.90-2.77 (1H, m), 2.03-1.60 (2H, m), 1.52-1.35 (2H, m); 75 MHz ¹³C NMR (CDCl₃) δ major diastereomer: 187.7, 186.7, 149.4, 137.1, 136.3, 132.8, 100.9, 65.8, 55.6, 33.4, 28.5, 24.7; minor diastereomer: 187.7, 186.6, 149.4, 137.1, 136.3, 132.8, 100.9, 65.8, 55.6, 33.4, 28.5, 24.7.
To a solution of 2 (34 mg, 0.126 mmol) in MeOH (3 mL) were added HgCl₂ (34 mg, 0.126 mmol) and I₂ (3 mg, 0.013 mmol) at rt. After being stirred at 60 °C for 3 h, the reaction mixture was evaporated in vacuo. The resulting residue was diluted with ethyl acetate and washed with brine. The aqueous layer was extracted with ethyl acetate one more time. The organic layer was dried over MgSO₄, filtered, and evaporated to dryness. The residue was purified by sgc (H:EA = 2:1) to give 40 (26.5 mg, 70%). 300 MHz ¹H NMR (CDCl₃) δ 6.94 (1H, d, J = 8.4 Hz), 6.48 (1H, dd, J = 8.4, 2.4 Hz), 6.47 (1H, d, J = 1.2 Hz), 6.37 (1H, d, J = 2.4 Hz), 5.89 (1H, d, J = 2.4 Hz), 4.27 (1H, ddd, J = 10.8, 2.7, 0.9 Hz), 4.06 (1H, ddd, J = 10.5, 6.3, 1.2 Hz), 3.83 (3H, s), 3.75 (3H, s), 3.53-3.40 (1H, m), 3.04 (1H, dd, J = 15.9, 5.7 Hz), 2.74 (1H, dd, J = 15.6, 6.9 Hz); 75 MHz ¹³C NMR (CDCl₃) δ 187.3, 181.6, 159.6, 159.0, 154.8, 146.5, 133.6, 130.3, 112.2, 108.3, 107.5, 101.8, 68.3, 56.6, 55.5, 31.1, 29.1; HRMS m/z for C₁₂H₁₄O₄ calcd 222.0892, found 222.0897.

2-(3,4-Dihydro-7-methoxybenzopyran-3-yl)-6-methoxy-1,4-benzoquinone (40)

To a solution of 2 (34 mg, 0.126 mmol) in MeOH (3 mL) were added HgCl₂ (34 mg, 0.126 mmol) and I₂ (3 mg, 0.013 mmol) at rt. After being stirred at 60 °C for 3 h, the reaction mixture was evaporated in vacuo. The resulting residue was diluted with ethyl acetate and washed with brine. The aqueous layer was extracted with ethyl acetate one more time. The organic layer was dried over MgSO₄, filtered, and evaporated to dryness. The residue was purified by sgc (H:EA = 2:1) to give 40 (26.5 mg, 70%). 300 MHz ¹H NMR (CDCl₃) δ 6.94 (1H, d, J = 8.4 Hz), 6.48 (1H, dd, J = 8.4, 2.4 Hz), 6.47 (1H, d, J = 1.2 Hz), 6.37 (1H, d, J = 2.4 Hz), 5.89 (1H, d, J = 2.4 Hz), 4.27 (1H, ddd, J = 10.8, 2.7, 0.9 Hz), 4.06 (1H, ddd, J = 10.5, 6.3, 1.2 Hz), 3.83 (3H, s), 3.75 (3H, s), 3.53-3.40 (1H, m), 3.04 (1H, dd, J = 15.9, 5.7 Hz), 2.74 (1H, dd, J = 15.6, 6.9 Hz); 75 MHz ¹³C NMR (CDCl₃) δ 187.3, 181.6, 159.6, 159.0, 154.8, 146.5, 133.6, 130.3, 112.2, 108.3, 107.5, 101.8, 68.3, 56.6, 55.5, 31.1, 29.1; HRMS m/z for C₁₂H₁₄O₄ calcd 222.0892, found 222.0897.

2-(3,4-Dihydro-7-methoxybenzopyran-3-yl)-6-phenylthio-1,4-benzoquinone (41a) and 2-(3,4-Dihydro-7-methoxybenzopyran-3-yl)-5-phenylthio-1,4-benzoquinone (41b)

To a mixture of 2 (83 mg, 0.307 mmol) and PhSH (35 µL, 0.338 mmol) in MeOH (10 mL) was added PTSA-H₂O (117 mg, 0.614 mmol) at rt. After being stirred at rt for 7 h, the reaction mixture was evaporated in vacuo. The resulting residue was diluted with CH₂Cl₂ and washed with brine. The aqueous layer was dried over MgSO₄, filtered, and evaporated to dryness. The residue was purified by sgc (H:EA = 3:1) to afford a regioisomeric mixture of hydroquinones (108.8 mg, 93%). The mixture of hydroquinones (108.8 mg, 0.286 mmol) was
dissolved in benzene (10 mL). Then, Na$_2$SO$_4$ (81 mg, 0.572 mmol) and Ag$_2$O (133 mg, 0.572 mmol) were added at rt. After being stirred at rt for 4 h, the mixture was filtered through Celite and rinsed with ethyl acetate. The filtrate was evaporated and purified by sgc (H:EA = 10:1) to give minor product (41b) and major product (41a) (total 108 mg, 100%).

**41a:** 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.49 (5H, br s), 6.95 (1H, d, $J$ = 8.4 Hz), 6.48 (1H, dd, $J$ = 8.4, 2.4 Hz), 6.44 (1H, dd, $J$ = 2.1, 0.9 Hz), 6.37 (1H, d, $J$ = 2.7 Hz), 5.84 (1H, d, $J$ = 2.4 Hz), 4.28 (1H, dd, $J$ = 10.5, 2.4 Hz), 4.09 (1H, dd, $J$ = 10.8, 6.3 Hz), 3.75 (3H, s), 3.55-3.42 (1H, m), 3.07 (1H, dd, $J$ = 16.2, 6.0 Hz), 2.75 (1H, dd, $J$ = 16.2, 6.6 Hz); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 184.6, 183.9, 159.6, 155.0, 154.9, 148.0, 135.9, 133.9, 130.8, 130.6, 130.4, 127.4, 126.1, 112.2, 108.3, 101.8, 68.3, 55.5, 31.4, 29.1; HRMS $m/z$ for C$_{22}$H$_{18}$O$_4$S calcd 378.0926, found 378.0931; TLC (3:1 H:EA) $R_f$ = 0.36.

**41b:** 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.50 (5H, br s), 6.94 (1H, d, $J$ = 8.4 Hz), 6.74 (1H, d, $J$ = 1.2 Hz), 6.48 (1H, dd, $J$ = 8.4, 2.4 Hz), 6.37 (1H, d, $J$ = 2.4 Hz), 5.89 (1H, s), 4.23 (1H, ddd, $J$ = 10.8, 3.0, 0.9 Hz), 4.04 (1H, ddd, $J$ = 10.8, 6.0, 0.9 Hz), 3.76 (3H, s), 3.45-3.35 (1H, m), 3.02 (1H, dd, $J$ = 15.9, 5.7 Hz), 2.72 (1H, dd, $J$ = 16.2, 6.9 Hz); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 184.3, 183.9, 159.6, 154.9, 154.6, 149.7, 135.9, 132.4, 130.8, 130.6, 130.3, 127.2, 126.3, 112.2, 108.3, 101.8, 68.4, 55.6, 31.2, 29.1; HRMS $m/z$ for C$_{22}$H$_{18}$O$_4$S calcd 378.0926, found 378.0931; TLC (3:1 H:EA) $R_f$ = 0.42.

**2-(3,4-Dihydro-7-methoxybenzopyran-3-yl)-6-phenylsulfinyl-1,4-benzoquinone (42)**

To a solution of 41a (35 mg, 0.093 mmol) in CHCl$_3$ (3 mL) was added 77% mCPBA (23 mg, 0.102 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. The mixture was diluted with CH$_2$Cl$_2$ and washed with saturated NaHCO$_3$ solution. The aqueous layer was extracted with CH$_2$Cl$_2$ one more time. The combined organic layers were dried over MgSO$_4$, filtered,
and concentrated. The crude residue was purified by sgc (H:EA = 3:1) to give sulfoxide 42 (35 mg, 96%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.88-7.74 (2H, m), 7.61-7.45 (3H, m), 7.45-7.36 (1H, m), 6.94 and 6.87 (1H, d, $J = 8.7$ Hz), 6.62-6.52 (1H, m), 6.52-6.42 (1H, m), 6.40-6.29 (1H, m), 4.24 and 4.12 (1H, dd, $J = 10.5, 2.1$ Hz), 4.05 and 3.90 (1H, dd, $J = 10.8, 6.0$ Hz), 3.74 (3H, s), 3.40-3.25 (1H, m), 3.06 and 2.96 (1H, dd, $J = 16.2, 6.3$ Hz), 2.70 and 2.61 (1H, dd, $J = 16.2, 6.3$ Hz); HRMS m/z for C$_{22}$H$_{18}$O$_5$S calcd 394.0875, found 394.0882.

References


and references cited therein.


17. A similar approach was used during the synthesis of tetrugol: Brown, P. M.; Thompson, R. H. *J. Chem. Soc., Perkin Trans 1* **1976**, *997*.


CHAPTER 3. 1,2-DIHALIDES IN ORGANIC SYNTHESIS:
A DIRECT SYNTHESIS OF EROGORIAENAE

Introduction

Rodriguez reported in 1999 that pseudopteroxazole and seco-pseudopteroxazole, isolated from the West Indian gorgonian octocoral *Pseudopterogorgia elisabethae*, exhibited potent and moderate antimycobacterial activity, respectively. More recently, two new serrulatane diterpenes, erogorgiaene and 7-hydroxyerogorgiaene, were also isolated from the same marine source.

![Chemical structures of pseudopteroxazole, seco-pseudopteroxazole, erogorgiaene, and 7-hydroxyerogorgiaene](image)

Despite their relatively simple structures, erogorgiaene and 7-hydroxyerogorgiaene showed very strong antitubercular activity. Thus, erogorgiaene induced 96% growth inhibition for *Mycobacterium tuberculosis* H37Rv at the microgram per milliliter level, a level comparable to that of pseudopteroxazole. As part of our continuing synthetic studies on
antitubercular serrulatane diterpenes, we embarked on the synthesis of erogorgiaene and its analogs.

**Results and Discussion**

As illustrated in the retrosynthetic scheme, erogorgiaene would be accessible from bromobenzene 1 via a 6-exo trig radical cyclization. The methyl group at the benzylic position of the radical precursor 1 could be installed from alcohol 2, which in turn could be derived from the addition of 2-bromophenyl lithium to aldehyde 3. 2-Bromophenyl lithium species would be obtainable from 2-bromo-1-iodo-4-methylbenzene 4 by way of a regioselective halogen-metal exchange. This strategy is based on the regioselective 1,2-functionalization of 1,2-dihalobenzene derivatives.

Aromatic halides have been generally considered a useful source for organolithium, radical, or palladium chemistry in organic synthesis. Therefore, if we could selectively functionalize one halogen over the other for symmetrical or unsymmetrical 1,2-
dihalobenzenes, different groups could be introduced at each halogen position.

Since the pioneering work on the ortho-halophenyl lithium species by Gilman,\(^4\) there aren’t many synthetic applications of this chemistry, which may be, in part, ascribed to the low temperatures required to generate this species. In 1980, Chen and Tamborski reported the reaction of ortho-bromophenyl lithium with several electrophiles to furnish 2-substituted bromobenzenes.\(^4\)

They prepared ortho-bromophenyl lithium by treatment of 1,2-dibromobenzene with \(n\)-BuLi at \(-110^\circ\)C. They claimed that this species was stable at \(-110^\circ\)C for at least 2 h.\(^4\)

To test the feasibility of our strategy, we first employed the commercially available 1,2-dibromobenzene. Aldehyde 3 was prepared as an E/Z mixture from the Claisen
rearrangement of linalool.\textsuperscript{5}

\[
\begin{array}{c}
\text{linalool} \\
\begin{array}{c}
\text{HO} \\
\text{Br} \\
\text{Br} \\
\text{Br}
\end{array}
\end{array}
\xrightarrow{Hg(OAc)\textsubscript{2} \ 140 \ ^\circ \text{C} \ 70 \ %}
\begin{array}{c}
\text{3}
\end{array}
\]

Treatment of 1,2-dibromobenzene with \textit{n}-BuLi at \(-110 \ ^\circ \text{C}\) followed by the addition of aldehyde 3 afforded benzyl alcohol 5 in 95\% yield.\textsuperscript{4b} In order to introduce the methyl group onto the benzylic position of 5, 5 was directly treated with trimethylaluminum.\textsuperscript{6} Surprisingly, no reaction occurred.

As an another attempt to install the methyl group onto benzylic position, benzyl alcohol 5 was first oxidized to the corresponding ketone using PCC. MeLi addition took place uneventfully to provide 7. However, tertiary alcohol 7 under ionic hydrogenolysis condition (Et\textsubscript{3}SiH, BF\textsubscript{3}-Et\textsubscript{2}O)\textsuperscript{7} did not give rise to 6, resulting in a complex mixture. Adoption of Sakai's procedure (TMSCI, NaI, and CH\textsubscript{3}CN)\textsuperscript{8} did not lead to the desired product, either.
Finally, we resorted to a two-step procedure in which alcohol 5 was acetylated to make a better leaving group. Exposure of the resulting acetate 8 to Me₃Al from -78 °C to rt provided 6 in excellent overall yield.

Overall, the three-step sequence supplied the radical precursor 6 without difficulty. Now, the stage is set for the key radical cyclization. The modeling of stereoselective 6-exo cyclizations is not as advanced as that of 5-exo systems. However, chair-like models for 6-exo cyclizations account for many observations.

The chair-E transition structure places the radical acceptor in an equatorial-like orientation while this group is axial-like in the chair-A transition state. Introduction of a substituent on a carbon on the chain (C1-C5) then generates two pairs of transition states (chair-E, axial and equatorial, and chair-A, axial and equatorial). Other things being equal, the model predicts that the major product should derive from the transition state where both the acceptor and the substituent are equatorial (chair-E-equatorial). Thus, chair-E-model predicts cis products from 2- and 4-substituted radicals, and trans products from 1-, 3-, and 5-substituted radicals. However, stereoselectivities in many simple carbocyclic systems are
low as demonstrated by Hanessian and coworkers.\textsuperscript{11}

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} \\
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{array}{ccc}
\text{E, } R = \text{Me} & \text{cis} & 35 \\
\text{E, } R = \text{t-Bu} & \text{trans} & 35 \\
\text{Z, } R = \text{t-Bu} & \text{cis} & 10 \\
\text{Z, } R = \text{t-Bu} & \text{trans} & 90
\end{array}
\]

Compound 6 was subjected to the standard \textit{n}-\text{Bu}_3\text{SnH}-mediated radical conditions to give 9 as well as other isomers in 73\% overall yield.

\[
\begin{array}{ccc}
\text{Br} & \text{Br} & \text{Br} \\
\text{Br} & \text{Br} & \text{Br}
\end{array}
\]

Based on the previous studies on radical cyclizations,\textsuperscript{10} the major product would be expected to have a trans relationship between the methyl group and the eight-carbon side chain.

\[
\begin{array}{ccc}
\text{H} & \text{H} & \text{H} \\
\text{H} & \text{H} & \text{H}
\end{array}
\]

The configuration at C11 was expected to be a mixture. The ratio of trans to cis products was about 1.5 to 1 by crude \textsuperscript{1}NMR analysis. Other radical initiators such as \textit{Et}_3\text{B}\textsuperscript{12} and \textit{SmL}_2\textsuperscript{13} were tested to increase the selectivity. However, they failed to provide better results. With
this information on radical cyclization in hand, attention was paid to regioselective halogen-metal exchange.

\[
\begin{array}{c}
\text{H}_2\text{N} \\
\text{Br} \\
\text{Br} \\
\text{Br}
\end{array}
\Rightarrow
\begin{array}{c}
\text{Br} \\
\text{Br} \\
\text{Br} \\
\text{Li}
\end{array}
\]

To examine this idea, 4 was prepared from 2-bromo-4-methylaniline in one step.\(^{14}\)

![Reaction scheme](image)

Reaction of 4 with \(n\)-BuLi at \(-110^\circ\text{C}\) in 1:1 THF:ether followed by the addition of aldehyde 3 delivered benzyl alcohol 2 in 86% isolated yield. By the similar two-step sequence, 2 was converted to radical precursor 1.

Again, a 6-exo-trig radical cyclization of bromide 1 with \(\text{Ph}_3\text{SnH}\) and AIBN in boiling benzene led to a mixture of erogorgiaene and its isomers in 70% overall yield.

![Cyclization reaction](image)

The ratio of trans to cis products was roughly 1.5 to 1 by crude \(^1\text{H-NMR}\) analysis. The separation of erogorgiaene from the product mixture was partially achieved by preparative
TLC on a AgNO₃ impregnated silica gel plate. The NMR of the purified product was identical to the NMR supplied by Professor Rodriguez.

In a similar manner, calamenene was also synthesized. To this end, aldehyde 10 was obtained from the Claisen rearrangement of 2-methyl-3-buten-2-ol.

\[
\begin{align*}
\text{CH}_2=\text{CH}-\text{CH}=&\text{CH} \quad \text{Hg(OAc)}_2 \\
150^\circ \text{C}, &\text{68%}
\end{align*}
\]

With this aldehyde 10 in hand, radical precursor 12 was prepared by following the same sequence we used before.

\[
\begin{align*}
\text{OH} &\quad \text{Br} \\
\text{Br} &\quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
n-\text{BuLi}, -110^\circ \text{C} &\quad 4, 84\% \\
10, 84\% &\quad 1) \text{Ac}_2\text{O}, \text{DMAP} \\
1\text{) Ac}_2\text{O}, \text{DMAP} &\quad 2) \text{Me}_3\text{Al}, -78^\circ \text{C to rt} \\
&\quad 12, 87\% \text{ over two steps}
\end{align*}
\]

The trans product was again obtained as a major isomer in the radical cyclization. The ratio of trans to cis isomers was about 1.5 to 1 by crude $^1\text{H}$ NMR analysis.

\[
\begin{align*}
\text{Br} &\quad \text{Ph}_3\text{SnH}, \text{cat. AlBN} \\
\text{benzene}, 85^\circ \text{C} &\quad 68\%
\end{align*}
\]

\[
\begin{align*}
\text{Br} &\quad \text{Ph}_3\text{SnH}, \text{cat. AlBN} \\
\text{benzene}, 85^\circ \text{C} &\quad 68\%
\end{align*}
\]

\[
\begin{align*}
\text{trans-calamenene} &\quad \text{cis-calamenene}
\end{align*}
\]

At this point different methodologies were sought to increase the stereoselectivity during cyclization. Thus, an intramolecular Heck reaction of bromide 1 was explored. We anticipated that the benzylic double bond of the product could be later reduced in a stereo-
and regioselective way.

In general, electron-rich aromatic bromides are not good substrates for palladium-catalyzed Heck type process. After several attempts using different palladium catalyst conditions were not fruitful, we found out that cyclization occurred under Herrmann’s catalyst condition.\textsuperscript{18} However, a mixture of alkenes was produced as a result of nonselective palladium-hydride elimination.

In line with the idea that double bond generation during cyclization and subsequent stereoselective incorporation of methyl group to this double bond could lead to the target compound more effectively, we devised radical precursors, vinyl sulfide 14 or alkynyl precursor.
Vinyl sulfide 14 was prepared from phenyl vinyl sulfide in two steps in reasonable yield. Thus, treatment of phenyl vinyl sulfide with n-BuLi in the presence of TMEDA and subsequent addition of aldehyde 10 furnished 15 in 88% yield.\(^\text{19}\) Claisen rearrangement of 15 in a sealed tube afforded aldehyde 16.

\[
\text{PhS} = \text{n-BuLi, TMEDA, } -78^\circ\text{C, 10} \quad \rightarrow \quad \begin{array}{c}
\text{PhS} \\
\text{O}
\end{array}
\]

\[
\begin{array}{c}
\text{88%} \\
\text{Hg(OAc)}_2 \\
150^\circ\text{C, 71%}
\end{array}
\]

\[\text{15} \quad \text{16}\]

Reaction of 4 with n-BuLi and subsequent treatment with 16 provided alcohol 17 which was acetylated and then exposed to Me\(_3\)Al to give 14. Unfortunately, radical cyclization did not occur.

\[
\text{I} \\
\text{Br}
\]

\[
\text{Br} \\
\text{Br}
\]

\[
\text{n-BuLi, -110}^\circ\text{C, 16, 80%} \quad \rightarrow \quad \begin{array}{c}
\text{PhS} \\
\text{O}
\end{array}
\]

\[
\begin{array}{c}
\text{OH} \\
\text{Br}
\end{array}
\]

\[
\text{1} \quad \text{17}
\]

\[
\text{1) Ac}_2\text{O, DMAP} \\
\text{2) Me}_3\text{Al, -78}^\circ\text{C to rt} \quad \rightarrow \quad \begin{array}{c}
\text{89% over two steps}
\end{array}
\]

Therefore, we decided to form the cyclic ketone first and to elaborate the bottom side chain later.
Toward this end, ketoester 18 was obtained from Friedel-Crafts acylation of toluene with succinic anhydride and subsequent esterification. Olefination of 18 followed by reduction of the exomethylene group gave ester 19. Ester 19 was hydrolyzed to acid which, upon exposure to trifluoroacetic anhydride/trifluoroacetic acid, underwent smooth cyclization to form cyclic ketone 20 in good yield.

Ketone 20 was subjected to Wittig olefination followed by the hydrolysis of the resulting enol ether to give aldehyde 21 in a 1:1 mixture. This result was in contrast with our expectation that trans product would be favored.

To see the cis/trans ratio of products derived from ketone 20, ketone 20 was first...
methylenated to give 22. PhSH addition to 22 under radical condition again led to a 1:1 mixture of products.

\[
\begin{align*}
\text{Ph}_3\text{P}=\text{CH}_2 & \xrightarrow{99\%} \text{Ph}_3\text{P}=\text{CH}_2 \text{PhSH} \text{, cat. AIBN} \text{ benzene, 95\%} \\
& \xrightarrow{99\%} \text{Ph}_3\text{P}=\text{CH}_2 \text{PhS} \\
20 & \xrightarrow{22} 22 & \xrightarrow{23} 23
\end{align*}
\]

Dissolving metal reduction of 22 provided a 3:1 trans:cis mixture 24.

\[
\begin{align*}
\text{Li, liq. NH}_3 & \xrightarrow{92\%} \text{Li, liq. NH}_3 \\
& \xrightarrow{92\%} \text{Li, liq. NH}_3 \\
22 & \xrightarrow{24} 24
\end{align*}
\]

To introduce the alkyl chain, a photochemical reaction was carried out. The intermolecular addition failed to occur.

\[
\begin{align*}
(n\text{-Bu}_3\text{Sn})_2, \text{hv} & \xrightarrow{10:1} (n\text{-Bu}_3\text{Sn})_2, \text{hv} \\
& \xrightarrow{10:1} (n\text{-Bu}_3\text{Sn})_2, \text{hv} \\
22 & \xrightarrow{22} 22 & \xrightarrow{27} 27
\end{align*}
\]

From these series of experimentations, we tentatively concluded that stereoselective introduction of alkyl side chain by nucleophilic or radical additions to ketone 20 or alkene 22 would be hard to achieve. We decided to make analogs of ergororgiaene to test their biological activity. Thus, ketones 26a, 26b, and 20 were reacted with lithiated phenylsulfone in the presence of Et_2AlCl to give hydroxy sulfones 27a, 27b, and 27c in good yields. Dissolving metal reduction of 27a, 27b, and 27c provided analogs of ergororgiaene, 29a, 29b, and 29c along with benzylic alcohols, 28a, 28b, and 28c. These benzylic alcohols were further treated with Li-NH\textsubscript{3} (liq.) to give analogs. Interestingly, the ratio of isomers is 2:1 with the
trans product as the major when \( R_1 \) is CH\(_3\). These analogs as well as stereomixture of erogorgiaene were submitted for biological testing.

\[
\begin{align*}
R_1 = R_2 = H: \text{(26a)} \\
R_1 = H, R_2 = \text{Me}: \text{(26b)} \\
R_1 = R_2 = \text{Me}: \text{(20)}
\end{align*}
\]

In summary, a direct synthesis of erogorgiaene was achieved employing a regioselective halogen-metal exchange and a 6-exo-trig radical cyclization as key steps. This strategy could be useful to the synthesis of other benzene-fused natural products. Several other possible routes to this diterpene were also examined. In addition, three analogs of erogorgiaene were prepared for comparison of their antitubercular activity.

**Experimental Section**

Unless otherwise noted, materials were obtained from commercial suppliers and used
without purification. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane and benzene were distilled over calcium hydride. All experiments were performed under argon atmosphere unless otherwise noted. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or Bruker 400 MHz instrument. All chemical shifts are reported relative to CDCl₃ (7.26 ppm for H and 77.06 ppm for ¹³C), unless otherwise noted. Coupling constants (J) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer and low resolution mass spectra were performed with a Finnegan 4023 mass spectrometer. Standard grade silica gel (60 Å, 32-63 μm) was used for a flash column chromatography.

(4E/Z)-5,9-Dimethyldeca-4,8-dienal (3)

A mixture of linalool (3.00 g, 19.45 mmol) and Hg(OAc)₂ (1.24 g, 3.89 mmol) in ethyl vinyl ether (19 mL, 194.5 mmol) was heated in sealed tube at 140 °C overnight. After being cooled to rt, K₂CO₃ (538 mg, 3.89 mmol) was added to this mixture. The mixture was suction-filtered through Celite and washed with n-hexane. The filtrate was evaporated in vacuo. The residue was purified by sgc (H:EA = 30:1) to give 3 (2.45 g, 70%). 300 MHz ¹H NMR (CDCl₃) δ 9.75 (1H, s), 5.17-5.02 (2H, m), 2.53-2.40 (2H, m), 2.40-2.26 (2H, m), 2.18-1.88 (5H, m), 1.76-1.50 (8H, m).

(4E/Z)-1-(2-Bromophenyl)-5,9-dimethyldeca-4,8-dien-1-ol (5)

To a solution of 1,2-dibromobenzene (1.23 g, 5.2 mmol) in THF (86 mL)/Et₂O (86 mL) was slowly added n-BuLi (2.5 M solution in hexanes, 2 mL, 5.2 mmol) at −110 °C (EtOH/liq. N₂ bath was used). After 30 min at −110 °C, a solution of 3 (1.2 g, 6.76 mmol) in THF (3 mL) was dropwise added to this mixture at −110 °C. After being stirred at −110 °C for 20 min, the
reaction mixture was allowed to warm to rt. The mixture was quenched with saturated NH₄Cl. The organic solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by sgc (H:EA = 30:1 to 20:1) to give 5 (1.67 g, 95%). 300 MHz ¹H NMR (CDCl₃) δ 7.54 (1H, d, J = 7.8 Hz), 7.49 (1H, d, J = 8.1 Hz), 7.31 (1H, t, J = 7.8 Hz), 7.10 (1H, t, J = 8.1 Hz), 5.28-5.00 (3H, m), 2.26-2.15 (2H, m), 2.15-1.75 (6H, m), 1.75-1.51 (9H, m); HRMS m/z for C₁₈H₂₅OBr calcld 336.1089, found 336.1093.

(5E/Z)-2-(2-Bromophenyl)-6,10-dimethylundeca-5,9-dien-2-ol (7)

To a solution of 5 (157 mg, 0.466 mmol) in CH₂Cl₂ (2 mL) was added PCC (121 mg, 0.559 mmol) at 0 °C. After being stirred at rt for 2 h, PCC (50 mg, 0.233 mmol) and Celite (160 mg) were added to this mixture. After being stirred at rt for additional 1 h, the mixture was diluted with Et₂O. The mixture was filtered through Celite and rinsed with Et₂O. The filtrate was evaporated in vacuo. The residue was purified by sgc (H:EA = 30:1) to afford ketone (135 mg, 87%). 300 MHz ¹H NMR (CDCl₃) δ 7.58 (1H, d, J = 7.8 Hz), 7.40-7.18 (3H, m), 5.14 (1H, t, J = 7.2 Hz), 5.13-5.01 (1H, m), 2.93 (2H, q, J = 7.2 Hz), 2.40 (2H, q, J = 7.2 Hz), 2.12-1.90 (4H, m), 1.73-1.50 (9H, m).

To a solution of MeLi (1.4 M solution in THF, 864 µL, 1.209 mmol) in THF (1 mL) was dropwise added a solution of ketone (135 mg, 0.403 mmol) in THF (1 mL + 1 mL for rinse) at -78 °C. After 5 min, the mixture was quenched with saturated NH₄Cl at -78 °C. The mixture was concentrated in vacuo. The residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo to give 7 (141 mg, 100%). 300 MHz ¹H NMR (CDCl₃) δ 7.73 and 7.71 (IH, dd, J = 7.8, 1.8 Hz), 7.57 and 7.56 (1H, d, J = 8.1 Hz), 7.31 and 7.30 (1H, t, J = 7.8 Hz), 7.09 and 7.08 (1H, t, J =
7.8 Hz), 5.21-5.00 (3H, m), 2.62-2.38 (2H, m), 2.15-1.36 (18H, m).

(4E/Z)-1-(2-Bromophenyl)-5,9-dimethyldeca-4,8-dienyl acetate (8)

To a solution of 5 (1.527 g, 4.53 mmol) in CH₂Cl₂ (15 mL) were added DMAP (664 mg, 5.436 mmol) and Ac₂O (513 μL, 5.436 mmol) at 0 °C. After being stirred at rt for 2 h, the mixture was concentrated in vacuo. The residue was diluted with ethyl acetate and washed with 10% HCl and saturated NaHCO₃ solution, successively. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 30:1 to 20:1) to give 8 (1.716 g, 100%). 300 MHz ¹H NMR (CDCl₃) δ 7.53 (1H, d, J = 7.2 Hz), 7.40-7.24 (2H, m), 7.12 (1H, t, J = 7.5 Hz), 6.05 (1H, t, J = 6.6 Hz), 5.20-5.10 (2H, m), 2.10 (3H, s), 2.15-1.90 (6H, m), 1.90-1.75 (2H, m), 1.73-1.50 (9H, m); HRMS m/z for C₂₀H₂₇O₂Br calcd 378.1194, found 378.1202.

1-Bromo-2-(1,5,9-trimethyldeca-4,8-dienyl)benzene (6)

To a solution of 8 (1.538 g, 4.06 mmol) in CH₂Cl₂ (46 mL) was dropwise added Me₃Al (2 M solution in hexanes, 7.1 mL, 14.21 mmol) at -78 °C. Then, the mixture was slowly warmed up to rt for 4 h. The mixture was quenched with saturated NH₄Cl at 0 °C. The mixture was suction-filtered through Celite and washed with CH₂Cl₂. The filtrate was evaporated in vacuo. The residue was purified by sgc (n-hexane only) to give 6 (1.29 g, 95%). 300 MHz ¹H NMR (CDCl₃) δ 7.53 (1H, d, J = 7.2 Hz), 7.36-7.15 (2H, m), 7.02 (1H, t, J = 8.4 Hz), 5.21-5.02 (2H, m), 3.37-3.20 (1H, m), 2.18-1.10 (20H, m); HRMS m/z for C₁₉H₂₇Br calcd 334.1296, found 334.1301.

1-(1,5-Dimethylhex-4-enyl)-4-methyl-1,2,3,4-tetrahydronaphthalene (9)

To a solution of 6 (81 mg, 0.242 mmol) in benzene (24.2 mL) were added n-Bu₃SnH (130 μL, 0.484 mmol) and AIBN (8 mg, 0.048 mmol) at rt. After being heated at 85 °C
overnight, the solvent was evaporated in vacuo. The residue was suspended in n-hexane, filtered through a short pad of silica gel, and washed with n-hexane. The filtrate was evaporated in vacuo. The residue was purified by prep TLC (H:EA = 100:1) to give a mixture of 9 and its isomers (46.8 mg, 75%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.35-7.05 (4H, m), 5.30-4.93 (1H, m), 3.00-2.60 (2H, m), 2.30-0.60 (21H, m).

2-Bromo-1-iodo-4-methylbenzene (4)

To an emulsion of 2-bromo-4-methylaniline (3 g, 16.12 mmol) in H$_2$O (4.1 mL) was slowly added c-HCl (4.1 mL) at rt. Then, a solution of NaNO$_2$ (1.22 g, 17.73 mmol) in H$_2$O (5.6 mL) was slowly added to the mixture at 0 °C. To the almost clear solution was slowly added a solution of KI (2.94 g, 17.73 mmol) in H$_2$O (3 mL) at 0 °C. After being stirred at rt for 4 h, the dark-colored reaction mixture was heated at 80 °C for 30 min. After being cooled to rt, the mixture was diluted with Et$_2$O and washed with 15% NaOH and saturated Na$_2$SO$_3$ solution, successively. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (n-hexane only) to afford 4 (3.59 g, 75%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.70 (IH, d, $J$ = 8.1 Hz), 7.45 (IH, d, $J$ = 1.8 Hz), 6.80 (1H, dd, $J$ = 8.1, 2.1 Hz), 2.28 (3H, s); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 140.1, 133.6, 129.8, 129.7, 97.2, 21.0.

(4E/Z)-1-(2-Bromo-4-methylphenyl)-5,9-dimethyldeca-4,8-dien-1-ol (2)

The same procedure for 5 was applied. 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.41 (1H, d, $J$ = 7.8 Hz), 7.34 (1H, s), 7.12 (1H, d, $J$ = 7.5 Hz), 5.26-4.98 (3H, m), 2.31 (3H, s), 2.50-1.50 (17H, m); HRMS m/z for C$_{19}$H$_{27}$OBr calcd 350.1245, found 350.1251.

2-Bromo-4-methyl-1-(1,5,9-trimethyldeca-4,8-diencyl)benzene (1)

The same procedures for 8 and 6 were applied.

Acetate: 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.38 (1H, d, $J$ = 2.1 Hz), 7.23 (1H, dd, $J$ = 8.1, 2.1
Hz), 7.09 (1H, d, J = 8.1 Hz), 6.01 (1H, t, J = 6.6 Hz), 5.20-5.00 (2H, m), 2.30 (3H, s), 2.50-1.50 (20H, m).

1: 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.45 (1H, d, J = 2.4 Hz), 7.19 (1H, dd, J = 7.8 Hz), 7.13 (1H, d, J = 8.1 Hz), 5.30-5.10 (2H, m), 3.42-3.24 (1H, m), 2.35 (3H, s), 2.20-1.50 (17H, m), 1.28 (3H, d, J = 6.9 Hz); HRMS m/z for C$_{20}$H$_{29}$Br calcd 348.1453, found 348.1460.

4-(1,5-Dimethylhex-4-enyl)-1,6-dimethyl-1,2,3,4-tetrahydronaphthalene (erogorgiaene) and its isomers

The same procedure for 9 was applied except the use of Ph$_3$SnH instead of $n$-Bu$_3$SnH.

300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.20-6.83 (3H, m), 5.21-4.90 (1H, m), 2.95-2.60 (2H, m), 2.30 (3H, s), 2.25-0.60 (21H, m).

5-MethyIhex-4-enal (10)

The same procedure for 3 was applied. 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 9.68 (1H, s), 5.02 (1H, t, J = 6.9 Hz), 2.45-2.32 (2H, m), 2.32-2.16 (2H, m), 1.61 (3H, s), 1.56 (3H, s).

1-(2-Bromo-4-methylphenyl)-5-methylhex-4-en-1-ol (11)

The same procedure for 5 was applied. 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.38 (1H, d, J = 8.1 Hz), 7.32 (1H, d, J = 0.9 Hz), 7.10 (1H, dd, J = 8.1, 1.2 Hz), 5.16 (1H, t, J = 7.2 Hz), 5.00 (1H, dd, J = 8.4, 4.2 Hz), 2.55 (1H, br s), 2.30 (3H, s), 2.14 (2H, q, J = 8.4 Hz), 1.87-1.56 (2H, m), 1.72 (3H, s), 1.62 (3H, s); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 141.0, 138.9, 133.2, 132.5, 128.7, 127.3, 124.1, 122.0, 72.7, 37.9, 26.0, 24.8, 20.9, 18.0; HRMS m/z for C$_{14}$H$_{19}$OBr calcd 282.0619, found 282.0624.

2-Bromo-1-(1,5-dimethylhex-4-enyl)-4-methylbenzene (12)

The same procedures for 8 and 6 were applied.

Acetate: 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.35 (1H, d, J = 0.9 Hz), 7.24 (1H, d, J = 7.8 Hz),
7.10 (1H, dd, J = 7.8, 0.9 Hz), 6.03 (1H, t, J = 6.3 Hz), 5.13 (1H, t, J = 6.9 Hz), 2.30 (3H, s),
2.09 (3H, s), 2.18-2.02 (2H, m), 1.90-1.76 (2H, m), 1.69 (3H, s), 1.58 (3H, s); 75 MHz $^{13}$C
NMR (CDCl$_3$) $\delta$ 170.2, 139.3, 137.7, 133.5, 132.7, 128.7, 127.0, 123.4, 122.2, 74.7, 35.8,
25.9, 24.4, 21.3, 20.9, 17.9.

12: 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.40 (1H, d, J = 0.3 Hz), 7.15 (1H, d, J = 7.8 Hz), 7.10 (1H,
dd, J = 8.1, 0.9 Hz), 5.15 (1H, t, J = 7.2 Hz), 3.35-3.20 (1H, m), 2.32 (3H, s), 2.10-1.85 (2H,
m), 1.71 (3H, s), 1.79-1.50 (2H, m), 1.56 (3H, s), 1.22 (3H, d, J = 6.9 Hz); 75 MHz $^{13}$C NMR
(CDCl$_3$) $\delta$ 143.4, 137.3, 133.4, 131.8, 128.7, 127.1, 124.9, 124.6, 37.6, 37.5, 26.3, 26.0, 21.6,
20.8, 17.9; HRMS m/z for C$_{15}$H$_{21}$Br calcd 280.0827, found 280.0832.

(1S, 4R)-4-Isopropyl-1,6-dimethyl-1,2,3,4-tetrahydronaphthalene ($trans$-calamenene)
and $cis$-calamenene

The same procedure for 9 was applied except the use of Ph$_3$SnH instead of n-Bu$_3$SnH.

300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.23-6.90 (3H, m), 3.00-2.60 (2H, m), 2.36 (3H, s), 2.40-0.70
(14H, m).

Mixture of alkenes (13)

To a solution of 1 (130 mg, 0.373 mmol) and n-Bu$_3$OAc (281 mg, 0.933 mmol) in DMF
(2 mL), CH$_3$CN (2 mL), and H$_2$O (0.4 mL) was added Herrmann's catalyst at 50 °C. After
being heated at 115 °C overnight, the mixture was cooled down to rt. The mixture was diluted
with Et$_2$O and washed with H$_2$O three times. The organic layer was dried over MgSO$_4$,
filtered, and evaporated in vacuo to give a mixture of alkenes. 300 MHz $^1$H NMR (CDCl$_3$) $\delta$
7.40-6.90 (3H, m), 5.35-5.13 (1H, m), 5.10-0.85 (24H, m).

7-Methyl-2-phenylthioocta-1,6-dien-3-ol (15)

To a solution of n-BuLi (2.5 M solution in hexanes, 3.5 mL, 8.81 mmol) and TMEDA
(1.1 mL, 7.34 mmol) in THF (24 mL) was added phenyl vinyl sulfide (960 μL, 7.34 mmol) at -78 °C. After being stirred at rt for 30 min, a solution of 10 (986 mg, 8.81 mmol) in THF (1 mL) was added to this mixture at -78 °C. After 5 min, the mixture was quenched with H2O. The organic solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO4, filtered, and concentrated in vacuo. The residue was purified by sgc (H:EA = 20:1 to 10:1) to give 15 (1.603 g, 88%). 300 MHz 1H NMR (CDCl3) δ 7.53-7.43 (2H, m), 7.38-7.23 (3H, m), 5.46 (1H, s), 5.13 (1H, t, J = 7.2 Hz), 4.92 (1H, s), 4.22 (1H, br s), 2.78 (1H, br s), 2.10 (2H, q, J = 7.5 Hz), 1.93-1.64 (2H, m), 1.69 (3H, s), 1.61 (3H, s); 75 MHz 13C NMR (CDCl3) δ 149.5, 133.7, 132.8, 132.4, 129.5, 128.2, 124.1, 112.9, 74.4, 36.4, 26.0, 24.5, 18.0.

(4E/Z)-9-Methyl-4-phenylthiodeca-4,8-dienal (16)

The same procedure for 3 was applied. 300 MHz 1H NMR (CDCl3) δ 9.66 (1H, s), 7.30-7.10 (5H, m), 5.98 (1H, t, J = 6.9 Hz), 5.13 (1H, t, J = 7.2 Hz), 2.65-2.55 (2H, m), 2.55-2.45 (2H, m), 2.40 (2H, q, J = 7.2 Hz), 2.11 (2H, q, J = 6.9 Hz), 1.70 (3H, s), 1.61 (3H, s).

(4E/Z)-1-(2-Bromo-4-methylphenyl)-9-methyl-4-phenylthiodeca-4,8-dien-1-ol (17)

The same procedure for 5 was applied. 300 MHz 1H NMR (CDCl3) δ 7.45-7.00 (8H, m), 5.99 (1H, t, J = 6.9 Hz), 5.19 (1H, t, J = 6.9 Hz), 5.03-4.90 (1H, m), 2.50-1.10 (8H, m), 2.32 (3H, s), 1.73 (3H, s), 1.64 (3H, s).

(6E/Z)-10-(2-Bromo-4-methylphenyl)-2-methyl-7-phenylthioundeca-2,6-diene (14)

The same procedures for 8 and 6 were applied.

Acetate: 300 MHz 1H NMR (CDCl3) δ 7.42-7.00 (8H, m), 6.07-5.85 (2H, m), 5.19 (1H, t, J = 6.9 Hz), 2.50-2.37 (2H, m), 2.37-1.90 (6H, m), 2.30 (3H, s), 2.20 (3H, s), 1.73 (3H, s), 1.64 (3H, s).
14: 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.45-6.95 (8H, m), 6.20-5.75 (1H, m), 5.25-5.05 (1H, m), 3.20-1.76 (9H, m), 2.30 (3H, s), 1.72 (3H, s), 1.62 (3H, s), 1.14 (3H, d, $J$ = 6.9 Hz).

**Methyl 4-oxo-4-p-tolybutyrate (18)**

To a mixture of toluene (50 mL, 469 mmol) and succinic anhydride (6.8 g, 68 mmol) was carefully added AlCl$_3$ (20 g, 150 mmol) at rt. After being heated to reflux for 1 h, the mixture was cooled down to rt. H$_2$O (50 mL) was added slowly over 10 min with care. After HCl gas evolution has ceased, the mixture was evaporated to remove toluene. The remaining residue was poured into cold H$_2$O in beaker. The solid formed was suction-filtered and rinsed with H$_2$O. The solid was dissolved in aqueous Na$_2$CO$_3$ solution. The mixture was filtered through Celite and washed with H$_2$O. The filtrate was acidified with c-HCl at 0 °C. The white solid formed was filtered, rinsed with H$_2$O, and dried under reduced pressure to afford acid (9.133 g, 70%). 300 MHz $^1$H NMR (acetone-d$_6$) $\delta$ 7.93 (2H, dd, $J$ = 8.1, 1.8 Hz), 7.33 (2H, d, $J$ = 8.4 Hz), 3.30 (2H, t, $J$ = 6.6 Hz), 3.24 (1H, br s), 2.70 (2H, t, $J$ = 6.6 Hz), 2.40 (3H, s),

A solution of the acid (16.7 g, 86.98 mmol) and c-H$_2$SO$_4$ (1 mL) in MeOH was heated to reflux with the occasional removal of H$_2$O and MeOH overnight (Dean-Stark trap was used). The mixture was concentrated in vacuo. The residue was diluted with ethyl acetate and washed with H$_2$O and saturated NaHCO$_3$ solution, successively. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo to give 18 (17.56 g, 98%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.88 (2H, d, $J$ = 8.4 Hz), 7.25 (2H, d, $J$ = 8.1 Hz), 3.70 (3H, s), 3.30 (2H, t, $J$ = 6.6 Hz), 2.75 (2H, t, $J$ = 6.6 Hz), 2.41 (3H, s).

**Methyl 4-p-tolylpentanoate (19)**

A suspension of methyltriphenylphosphonium bromide (17.5 g, 48.86 mmol) and t-BuOK (5.48 g, 48.86 mmol) in benzene (210 mL) was stirred under argon atmosphere at rt
for 4h. Then, a solution of 18 (8.388 g, 40.72 mmol) in benzene (80 mL + 4 mL for rinse) was transferred to this mixture at rt via cannula. After being stirred at rt overnight, the mixture was concentrated in vacuo. The residue was suspended in solvent (H:EA = 10:1), filtered through Celite, and washed with solvent (H:EA = 10:1). The filtrate was evaporated in vacuo. The residue was purified by sgc (H:EA = 100:1) to give alkene (7.808 g, 94%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.32 (2H, d, $J = 8.4$ Hz), 7.15 (2H, d, $J = 8.4$ Hz), 5.29 (1H, s), 5.05 (1H, s), 3.67 (3H, s), 2.90-2.76 (2H, m), 2.55-2.43 (2H, m), 2.35 (3H, s); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 173.8, 146.9, 137.8, 137.6, 129.3, 126.2, 112.2, 51.7, 33.3, 30.7, 21.3.

To a solution of the alkene (12.213 g, 59.87 mmol) in ethyl acetate was carefully added 10% Pd/C (1.2 g) at rt. After being stirred under H$_2$ balloon at rt for 7 h, the mixture was suction-filtered through Celite and rinsed with ethyl acetate. The filtrate was evaporated in vacuo to give 19 (12.333 g, 100%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.14 (2H, d, $J = 8.4$ Hz), 7.10 (2H, dd, $J = 8.4$, 2.1 Hz), 3.65 (3H, s), 2.82-2.65 (1H, m), 2.35 (3H, s), 2.30-2.16 (2H, m), 2.05-1.83 (2H, m), 1.29 (3H, d, $J = 6.9$ Hz); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 174.3, 143.4, 135.8, 129.4, 127.1, 51.6, 39.2, 33.5, 32.5, 22.5, 21.2.

4,7-Dimethyl-3,4-dihydro-2H-naphthalen-1-one (20)

A mixture of 19 (9.953 g, 48.3 mmol) and NaOH (3.9 g, 96.6 mmol) in H$_2$O (100 mL) and MeOH (25 mL) was heated to reflux for 30 min. After being cooled down to rt, MeOH was evaporated in vacuo. The mixture was acidified with c-HCl at 0°C. The mixture was extracted with ethyl acetate and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo to afford acid (9.2 g, 99%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.19 (2H, d, $J = 8.1$ Hz), 7.14 (2H, d, $J = 8.4$ Hz), 2.90-2.70 (1H, m), 2.40 (3H, s), 2.38-2.26 (2H, m), 2.10-1.85 (2H, m), 1.34 (3H, d, $J = 6.9$ Hz); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 180.9,
143.3, 136.0, 129.5, 127.2, 39.2, 33.3, 32.7, 22.6, 21.3.

To the acid (8.26 g, 43.02 mmol) in TFA (43 mL) was added TFAA (9.1 mL, 64.53 mmol) at 0 °C. After being stirred at 0 °C for 2 h, the mixture was quenched with cold H₂O and saturated NaHCO₃ solution at 0 °C. When the aqueous phase was neutral or basic, the mixture was extracted with CH₂Cl₂ and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 20:1 to 10:1) to give 20 (7.11 g, 95%). 300 MHz ¹H NMR (CDCl₃) δ 7.80 (1H, s), 7.27 (1H, dd, J = 7.8, 2.1 Hz), 7.17 (1H, d, J = 7.8 Hz), 3.10-2.92 (IH, m), 2.83-2.65 (IH, m), 2.62-2.45 (IH, m), 2.30 (3H, s), 2.26-2.10 (1H, m), 1.90-1.73 (1H, m), 1.33 (3H, d, J = 7.2 Hz); 75 MHz ¹³C NMR (CDCl₃) δ 198.7, 146.3, 136.3, 134.7, 131.8, 127.5, 36.7, 32.7, 31.0, 21.1, 20.9.

4,7-Dimethyl-1,2,3,4-tetrahydronaphthalene-1-carbaldehyde (21)

To a suspension of methoxymethyltriphenylphosphonium chloride (2.3 g, 6.792 mmol) in THF (7 mL) was added n-BuLi (2.5 M solution in hexanes, 2.3 mL, 5.66 mmol) at 0 °C. After 5 min at 0 °C, a solution of 20 (394 mg, 2.264 mmol) in THF (3 mL + 1 mL for rinse) was added to this mixture at 0 °C via cannula. After being stirred at rt for 4 h, the mixture was quenched with saturated NH₄Cl and evaporated in vacuo. The residue was dissolved in THF (5 mL) and TFA (500 μL) was added at 0 °C. After being heated at 85 °C for 8 h, the mixture was concentrated in vacuo. The residue was diluted with ethyl acetate and washed with saturated NaHCO₃ solution. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 30:1) to give 21 (298 mg, 70%). 300 MHz ¹H NMR (CDCl₃) δ 9.67 and 9.64 (IH, d, J = 2.1 Hz), 7.21 and 7.18 (1H, d, J = 8.1 Hz), 7.07 (1H, d, J = 7.8 Hz), 6.95 (1H, s), 3.60-3.50 (1H, m), 2.99-2.82 (1H, m), 2.33 (3H, s), 2.32-1.45 (4H, m), 1.29 and 1.27 (3H, d, J = 6.9 Hz).
1,6-Dimethyl-4-methylene-1,2,3,4-tetrahydronaphthalene (22)

The same procedure for 19 was applied. 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.70 (1H, s), 7.36 (1H, dd, $J = 7.8, 2.7$ Hz), 7.27 (1H, d, $J = 7.8$ Hz), 5.70 (1H, s), 5.18 (1H, s), 3.26-3.10 (1H, m), 2.97-2.80 (1H, m), 2.78-2.62 (1H, m), 2.56 (3H, s), 2.32-2.16 (1H, m), 1.95-1.78 (1H, m), 1.54 (3H, d, $J = 6.9$ Hz); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 144.4, 139.7, 135.5, 134.6, 129.3, 128.5, 125.2, 108.0, 33.5, 32.3, 30.8, 22.8, 21.6.

1,6-Dimethyl-4-phenylthiomethyl-1,2,3,4-tetrahydronaphthalene (23)

To a solution of 22 (103 mg, 0.599 mmol) were added AIBN (20 mg, 0.12 mmol) and PhSH (68 µL, 0.659 mmol) at rt. After being heated at 85 °C for 2 h, the mixture was concentrated in vacuo to give crude 23 (160 mg, 95%) as a 1:1 mixture. 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.57-6.90 (3H, m), 3.42-3.26 (1H, m), 3.17-3.05 (1H, m), 3.05-2.75 (2H, m), 2.31 (3H, s), 2.17-1.37 (4H, m), 1.32 and 1.24 (3H, d, $J = 6.9$ Hz).

1,4,6-Trimethyl-1,2,3,4-tetrahydronaphthalene (24)

To a solution of 22 (68.7 mg, 0.399 mmol) in THF (2 mL) was added gaseous NH$_3$ at -78 °C. Then, small pieces of Li metal (28 mg, 3.99 mmol) was added to this mixture at -78 °C. After being stirred at -78 °C for 30 min, the mixture was quenched with saturated NH$_4$Cl at -78 °C. The excess NH$_3$ was blown out using argon. The residue was diluted with Et$_2$O and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (n-hexane only) to give 24 (64 mg, 92%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.18 (1H, d, $J = 7.8$ Hz), 7.10 (1H, s), 7.03 (1H, dd, $J = 7.8, 1.8$ Hz), 3.05-2.85 (1H, m), 2.30 (3H, s), 2.15-1.46 (4H, m), 1.34-1.28 (6H, m)

(5-Methylhex-4-ene-1-sulfonyl)benzene (25)

To a solution of 10 (6.145 g, 54.87 mmol) in MeOH (100 mL) was added NaBH$_4$ (2 g,
54.87 mmol) at 0 °C. After being stirred at rt for 30 min, the mixture was quenched with saturated NH₄Cl at 0 °C. The organic solvent was evaporated in vacuo. The residue was diluted with CH₂Cl₂ and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo to give alcohol (5.4 g, 86%). 300 MHz ¹H NMR (CDCl₃) δ 5.20-5.05 (1H, m), 3.64 (2H, t, J = 6.3 Hz), 2.06 (2H, q, J = 7.2 Hz), 1.69 (3H, s), 1.63 (3H, s), 1.78-1.55 (2H, m), 1.40 (1H, br s).

To a solution of the alcohol (5.4 g, 47.4 mmol) in CH₂Cl₂ (100 mL) were added PPh₃ (13.7 g, 52.1 mmol) and CBr₄ (17.3 g, 52.1 mmol) at 0 °C (exothermic). After 10 min at 0 °C, the mixture was concentrated in vacuo. The residue was purified by sgc (H:EA = 30:1) to give bromide (7.54 g, 90%). 300 MHz ¹H NMR (CDCl₃) δ 5.08 (1H, t, J = 7.2 Hz), 3.40 (2H, t, J = 6.9 Hz), 2.13 (2H, q, J = 6.9 Hz), 1.97-1.83 (2H, m), 1.70 (3H, s), 1.63 (3H, s).

To a solution of bromide (2.63 g, 14.89 mmol) in DMF (15 mL) was added PhSO₂Na (2.9 g, 17.87 mmol) at rt. After being stirred at rt overnight, the mixture was diluted with ethyl acetate and washed with H₂O three times. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1 to 5:1) to give sulfoxide 25 (3.01 g, 85%). 300 MHz ¹H NMR (CDCl₃) δ 7.96-7.85 (2H, m), 7.72-7.62 (1H, m), 7.62-7.51 (2H, m), 4.98 (1H, t, J = 7.2 Hz), 3.15-3.02 (2H, m), 2.13-1.96 (2H, m), 1.85-1.70 (2H, m), 1.66 (3H, s), 1.55 (3H, s); 100 MHz ¹³C NMR (CDCl₃) δ 139.2, 133.7, 133.67, 129.3, 128.1, 122.2, 55.7, 26.5, 25.7, 22.9, 17.8.

**7-Methyl-3,4-dihydro-2H-naphthalen-1-one (26b)**

To a solution of 4-oxo-4-p-tolylbutyric acid (2.6 g, 13.54 mmol) and c-HCl (0.6 mL) in MeOH (45 mL) was carefully added 10% Pd/C (1.3 g) at rt. After being stirred at rt for 7 h, the mixture was filtered through Celite and rinsed with ethyl acetate. The filtrate was
evaporated in vacuo. The residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo to give methyl 4-p-tolylbutyrate (2.6 g, 100%). 400 MHz ¹H NMR (CDCl₃) δ 7.11 (2H, d, J = 8.0 Hz), 7.08 (2H, d, J = 8.0 Hz), 3.67 (3H, s), 2.63 (2H, t, J = 7.6 Hz), 2.34 (3H, s), 2.38-2.27 (2H, m), 2.03-1.88 (2H, m); 100 MHz ¹³C NMR (CDCl₃) δ 174.0, 138.4, 135.5, 129.1, 128.4, 51.5, 34.8, 33.4, 26.7, 21.1.

A mixture of methyl ester (3 g, 15.63 mmol) and NaOH (1.3 g, 31.26 mmol) in H₂O (45 mL) and MeOH (5 mL) was heated to reflux for 30 min. After being cooled to rt, the MeOH was evaporated in vacuo. The residue was acidified with c-HCl at 0 °C. The white solid formed was filtered, rinsed with H₂O, and dried under reduced pressure to provide 4-p-tolylbutyric acid (2.75 g, 99%). 400 MHz ¹H NMR (CDCl₃) δ 7.12 (2H, d, J = 8.0 Hz), 7.08 (2H, d, J = 8.0 Hz), 2.61 (2H, t, J = 7.2 Hz), 2.37 (3H, s), 2.33 (2H, t, J = 7.2 Hz), 2.00-1.85 (2H, m); 100 MHz ¹³C NMR (CDCl₃) δ 180.5, 138.6, 135.4, 129.2, 128.5, 34.9, 34.5, 26.8, 21.1.

To a solution of acid (1.83 g, 10.28 mmol) in TFA (10.28 mL) was added TFAA (2.2 mL, 15.42 mmol) at 0 °C. After being stirred at 0 °C for 2 h, the mixture was quenched with cold H₂O and saturated NaHCO₃ solution at 0 °C. The basic reaction mixture was diluted with CH₂Cl₂ and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 20:1 to 10:1) to afford 26b (1.62 g, 98%). 400 MHz ¹H NMR (CDCl₃) δ 7.80 (1H, s), 7.23 (1H, dd, J = 7.6, 1.2 Hz), 7.09 (1H, d, J = 7.6 Hz), 2.87 (2H, t, J = 6.0 Hz), 2.59 (2H, t, J = 6.4 Hz), 2.31 (3H, s), 2.15-2.02 (2H, m); 100 MHz ¹³C NMR (CDCl₃) δ 199.0, 141.7, 136.3, 134.4, 132.4, 128.7, 127.3, 39.3, 29.3, 23.5, 21.0.
1-(1-Benzensulfonyl-5-methylhex-4-enyl)-1,2,3,4-tetrahydronaphthalene-1-ol (27a)

To a solution of sulfone 25 (210 mg, 0.882 mmol) in THF (3 mL) was added n-BuLi (2.5 M solution in hexanes, 353 μL, 0.882 mmol) at −78 °C. After 5 min at −78 °C, a solution of α-tetralone 26a (117 μL, 0.882 mmol) in THF (1 mL + 0.5 mL for rinse) was transferred to this mixture at −78 °C via cannula. Then, Et₂AlCl (1.8 M solution in toluene, 490 μL, 0.882 mmol) was slowly added at −78 °C. After being stirred at −78 °C for 15 min, the mixture was quenched with saturated NH₄Cl, diluted with CH₂Cl₂, and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give 27a (319 mg, 94%). 300 MHz ¹H NMR (CDCl₃) δ 8.10-7.00 (9H, m), 4.40-4.25 (IH, m), 3.76-0.98 (17H, m); HRMS m/z for C₂₃H₂₅O₂S calcd 384.1759, found 384.1766.

1-(5-Methylhex-4-enyl)-1,2,3,4-tetrahydronaphthalene-1-ol (28a) and 1-(5-Methylhex-4-enyl)-1,2,3,4-tetrahydronaphthalene (29a)

To a solution of 27a (297 mg, 0.773 mmol) in Et₂O (3 mL) was added gaseous NH₃ at −78 °C. Then, small pieces of Li metal (54 mg, 7.73 mmol) was added to this mixture at −78 °C. After being stirred at −78 °C for 30 min, the mixture was quenched with saturated NH₄Cl at −78 °C. The excess NH₃ was blown out using argon. The residue was diluted with n-hexane and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by sgc (n-hexane only to H:EA = 15:1) to give 29a along with 28a. Benzyl alcohol 28a was further treated with Li/NH₃ at −30 °C for 30 min before quenching to give 29a.

28a: 400 MHz ¹H NMR (CDCl₃) δ 7.51 (1H, d, J = 7.6 Hz), 7.19 (1H, t, J = 7.2 Hz), 7.15 (1H, dt, J = 7.2, 1.6 Hz), 7.06 (1H, d, J = 7.2 Hz), 5.08 (1H, t, J = 7.2 Hz), 2.77-2.66 (2H, m),
2.09-1.15 (10H, m), 1.66 (3H, s), 1.57 (3H, s); 100 MHz $^{13}$C NMR (CDCl$_3$) δ 142.4, 136.8, 131.7, 128.9, 127.1, 126.3, 124.5, 72.5, 42.2, 36.1, 30.0, 28.4, 25.8, 24.5, 19.8, 17.8.

29a: 400 MHz $^1$H NMR (CDCl$_3$) δ 7.21-7.00 (4H, m), 5.15 (1H, t, $J = 7.2$ Hz), 2.76 (3H, br s), 2.13-1.94 (2H, m), 1.94-1.80 (2H, m), 1.77-1.30 (6H, m), 1.71 (3H, s), 1.62 (3H, s); 100 MHz $^{13}$C NMR (CDCl$_3$) δ 141.7, 137.1, 131.5, 129.1, 128.7, 125.5, 125.4, 124.8, 37.6, 36.7, 29.8, 28.3, 27.7, 27.5, 25.8, 19.9, 17.8; HRMS $m/z$ for C$_{17}$H$_{24}$ calcd 228.1878, found 228.1882.

1-(1-Benzencesulfonfyl-5-methylhex-4-enyl)-7-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (27b)

The same procedure for 27a was applied. 400 MHz $^1$H NMR (CDCl$_3$) δ 8.05-6.85 (8H, m), 4.48-4.27 (1H, m), 3.68-0.80 (20H, m).

7-MethyI-1-(5-methylhex-4-enyl)-1,2,3,4-tetrahydronaphtalen-1-ol (28b) and 7-MethyI-1-(5-methylhex-4-enyl)-1,2,3,4-tetrahydronaphthalene (29b)

The same procedure for 29a was applied.

28b: 400 MHz $^1$H NMR (CDCl$_3$) δ 7.32 (1H, s), 6.97 (2H, s), 5.17 and 5.12 (1H, t, $J = 7.2$ Hz), 2.87-2.62 (2H, m), 2.31 (3H, s), 2.10-1.19 (10H, m), 1.67 (3H, s), 1.58 (3H, s); 100 MHz $^{13}$C NMR (CDCl$_3$) δ 142.3, 135.7, 133.7, 131.7, 128.8, 128.0, 126.7, 124.6, 72.5, 42.1, 36.2, 29.6, 28.4, 25.8, 24.5, 21.3, 19.9, 17.8

29b: 400 MHz $^1$H NMR (CDCl$_3$) δ 6.98 (1H, s), 6.95 (1H, d, $J = 7.6$ Hz), 6.90 (1H, d, $J = 7.6$ Hz), 5.14 (1H, t, $J = 7.2$ Hz), 2.71 (3H, br s), 2.30 (3H, s), 2.11-1.93 (2H, m), 1.90-1.75 (2H, m), 1.75-1.31 (6H, m), 1.68 (3H, s), 1.62 (3H, s); 100 MHz $^{13}$C NMR (CDCl$_3$) δ 141.5, 134.8, 134.0, 131.4, 129.2, 129.0, 126.3, 124.8, 37.5, 36.7, 29.4, 28.3, 27.8, 27.5, 25.8, 21.2, 19.9, 17.8; HRMS $m/z$ for C$_{18}$H$_{36}$ calcd 242.2035, found 242.2038.
1-(1-Benzencesulfonyl-5-methylhex-4-enyl)-4,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (27c)

The same procedure for 27a was applied. 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 8.12-6.93 (8H, m), 4.58-4.25 (1H, m), 3.79-0.80 (22H, m).

4,7-Dimethyl-1-(5-methylhex-4-enyl)-1,2,3,4-tetrahydronaphthalen-1-ol (28c) and 1,6-Dimethyl-4-(5-methylhex-4-enyl)-1,2,3,4-tetrahydronaphthalene (29c)

The same procedure for 29a was applied.

28c: 400 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.34 (1H, s), 7.17-6.98 (2H, m), 5.12 (1H, br s), 2.99-2.71 (1H, m), 2.33 (3H, s), 2.19-1.37 (10H, m), 1.70 (3H, s), 1.60 (3H, s), 1.30 and 1.26 (3H, d, $J$ = 6.9 Hz).

29c: 400 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.22-6.94 (3H, m), 5.22 (1H, br s), 3.00-2.83 (1H, m), 2.83-2.70 (1H, m), 2.37 (3H, s), 2.19-1.39 (10H, m), 1.77 (3H, s), 1.69 (3H, s), 1.34 and 1.31 (3H, d, $J$ = 6.9 Hz); HRMS m/z for C$_{19}$H$_{28}$ calcld 256.2191, found 256.2194.

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CHAPTER 4. SYNTHETIC STUDIES TOWARDS ANTITUBERCULAR BENZOXAZOLE ALKALOIDS

Introduction

In 1999, Rodriguez and coworkers isolated pseudopteroxazole and seco-pseudopteroxazole from the hexane extracts of the West Indian gorgonian coral *Pseudopterogorgia elibethae* (Bayer) collected near San Andres Island, Colombia.\(^1\) While pseudopteroxazole exhibits potent inhibitory activity (97%) against *M. tuberculosis* H37Rv at a concentration of 12.5 \(\mu\)g/mL, seco-pseudopteroxazole inhibits 66% of mycobacterial growth.\(^1\) Initially, the structures of these two alkaloids were assigned as shown below.

\[
\begin{align*}
\text{pseudopteroxazole} & \quad \text{seco-pseudopteroxazole} \\
\end{align*}
\]

During the course of our synthetic investigations on the original structures of these natural products, Corey reported the enantiospecific total synthesis of pseudopteroxazole utilizing an intramolecular Diels-Alder reaction as a key step.\(^2\)

But NMR spectra of synthetic sample were inconsistent with the ones of natural product. Therefore, he proposed the revised structure of pseudopteroxazole based on his previous work on this family of diterpenes such as pseudopterosin\(^3\) and helioporin E.\(^4\)
To date no total synthesis of these two new structures has been reported.

Part of this section will describe our synthetic efforts towards the originally proposed structures of two antitubercular benzoxazole alkaloids.

**Results and Discussion**

Cis orientation of two alkyl chains at C4 and C7 positions of these natural products
inspired us to employ the Diels-Alder reaction of the diene with benzoquinone dienophile to construct the bicyclic core. To validate the feasibility of this strategy, compound 1 was chosen as a synthetic target. Synthetic analog 1 of seco-pseudopteroxazole would be elaborated from acetate 2 which, in turn, would be assembled from the known diene 3 and dienophile 4 by utilizing an intermolecular Diels-Alder cycloaddition.

In this context, diene 3 and dienophile 4 were prepared from the commercially available source, respectively. Thus, LAH reduction of 2,4-hexadienal provided dienol, which was acetylated to give 3 in good overall yield.\(^5\)

Formylation\(^6\) of 2,5-dimethoxyaniline gave formamide 5. Exposure of 5 to BBr\(_3\) afforded hydroquinone which was then oxidized to benzoquinone 4 in good yield.\(^7\)

Now, these two coupling partners set the stage for the key Diels-Alder transformation.
In 1985, our group reported the highly regioselective Diels-Alder reaction with the same diene 3.\(^5\)

\[
\begin{array}{c}
\text{AcO} \\
\text{CH}_2=CH- \\
\text{AcO}
\end{array} +
\begin{array}{c}
\text{AcO} \\
\text{E} = \text{CO}_2\text{Et}
\end{array} \rightarrow
\begin{array}{c}
\text{AcO} \\
\text{E} \\
\text{AcO}
\end{array} +
\begin{array}{c}
\text{AcO} \\
\text{H} \\
\text{AcO}
\end{array} \\
\text{3} \\
\text{E = CO}_2\text{Et} \\
\text{20}
\end{array}
\]

Based on this observation, we expected the similar or higher regioselectivity with diene 3 and dienophile 4. However, thermal Diels-Alder reaction of 3 and 4 provided an approximately 1.5:1 mixture of inseparable regioisomers in which the desired product was major. Hydroquinones 6a and 6b were also obtained along with the corresponding benzoquinones 5a and 5b from the reaction mixture in a 3:1 ratio, respectively.

\[
\begin{array}{c}
\text{AcO} \\
\text{CH}_3\text{CN/H}_2\text{O} \\
\text{reflux} \\
70\%
\end{array}
\]

Various attempts to improve the regioselectivity were unsuccessful. With this result in hand, we decided to transform the cycloadducts into the final target molecule. Thus, catalytic hydrogenation of the mixture 5a/b and 6a/b and subsequent treatment with PTSA-H\(_2\)O in boiling benzene/ethyl acetate gave rise to an inseparable mixture of benzoxazoles 7a and 7b.
Triflation of the phenol group of 7a/b provided 8a and 8b.\(^8\)

At this stage, these two regioisomers were separated by column chromatography. However, we were still not sure which one was our desired product. Unfortunately, the wrong isomer was first considered to be our desired product. A number of reactions had been carried out with the wrong isomer before the structure was unambiguously confirmed by X-ray crystallography. Although the results were not successful, I think that the reactions with isomer 8b are worthwhile to describe. The triflate group was removed under palladium catalyzed conditions\(^9\) to give 9 which was treated with K\(_2\)CO\(_3\) in methanol to furnish alcohol 10.

At this point, we carried out a model study to establish the method to install the alkyl side chain. Thus, cyclohexanecarboxaldehyde was treated with the lithium enolate of mesityl oxide at -78 °C to give β-hydroxy ketone 11 which, upon exposure to PTSA-H\(_2\)O in benzene at rt, was converted to unsaturated ketone 12. Regioselective Michael addition\(^10\) of cuprate to 12 in the presence of TMSCl at 0 °C produced enol ether 13 which was subsequently treated with TBAF to give enone 14.
With this successful result in hand, alcohol 10 was converted to the corresponding aldehyde 15 using PCC. Aldehyde 15 was reacted with the lithium enolate of mesityl oxide to provide aldol product 16 in modest yield. Acid treatment of 16 gave a complex mixture of products. This is probably due to the acidity of benzylic hydrogen which would cause epimerization and/or elimination of H₂O.

A different strategy was also tried to incorporate the alkyl side chain. Thus, Dess-Martin
oxidation of 10 gave aldehyde 15 which was treated with Wittig reagent $17^\text{11}$ in boiling methylene chloride to deliver 18. This compound would be prepared from aldehyde 15 by Wittig reaction followed by the isomerization of the double bond. Conducting the Wittig reaction at room temperature to avoid double bond migration also led to a mixture of diastereomers as a consequence of epimerization.

Thus, we sought to introduce the alkyl side chain by nucleophilic displacement.

Tosylation of 10 provided 20. However, many attempts to couple 20 with nucleophiles
under a variety of conditions were unsuccessful. Replacement of the tosyl group in 20 by iodide and the reaction of 21 with a cuprate did not afford the desired product.

Interestingly, a halogen-metal exchange of 21 followed by the addition of 4-methyl-3-pentenyl bromide gave the reduced product. Efforts to introduce the allyl, cyano, or phenylsulfonyl group on the iodide position led to the same alkene product 23 presumably because of the high acidity of the benzylic hydrogen.

The reaction of 21 with thiophenoxide afforded sulfide 24 which was oxidized to sulfoxide 25 using NaIO₄.
Unfortunately, the reaction of 25 with bromide did not furnish the desired product.

Finally, the reaction of lithium anion of sulfone 26 with iodide 21 at -78 °C led to a sulfone 27 as a mixture of diastereomers. However, subjection of 27 to 5% Na amalgam in MeOH provided a complex mixture.

While we were trying to resolve this problem, we envisaged that the side chain could be introduced at the cycloaddition stage. To this end, we designed diene 28.

This diene was prepared in two steps from mesityl oxide.
At this time, we used more reactive dienophile 30 for cycloaddition with this diene 28.

A Diels-Alder reaction of 28 and 30 gave adduct 31 in 65% yield. With the intent of reducing the unconjugated double bond selectively in the presence of double bonds conjugated to the carbonyl group, 31 was subjected to catalytic hydrogenation. However, this resulted in reduction of all of the double bonds. Next, another diene 32 bearing an alkynyl side chain was designed.

$p$-Methoxybenzyl alcohol was alkylated with propargyl bromide in the presence of NaH to give ether 33. Nucleophilic attack of lithium acetylide to 2,4-hexadienal led to propargyl
alcohol 34 in good yield. Acetylation of alcohol 34 provided diene 32.

$$\text{OMe} \quad 60\% \text{NaH, THF} \quad \longrightarrow \quad \begin{array}{c}
\text{Br} \\
\text{92\%}
\end{array} \quad \longrightarrow \quad \begin{array}{c}
\text{OPMB} \\
\text{95\%}
\end{array} \quad \longrightarrow \quad \begin{array}{c}
\text{HO} \\
\text{92\%}
\end{array} \quad \longrightarrow \quad \begin{array}{c}
\text{OPMB}
\end{array}$$

With this diene 32 in hand, a thermal Diels-Alder reaction was carried out. Unfortunately, the desired cycloadduct was not observed. Lewis acid catalyzed reaction destroyed the diene 32.

$$\text{AcO, pyr.} \quad \begin{array}{c}
\text{cat. DMAP, CH}_2\text{Cl}_2 \\
69\%
\end{array} \quad \longrightarrow \quad \begin{array}{c}
\text{AcO} \\
\text{69\%}
\end{array} \quad \longrightarrow \quad \begin{array}{c}
\text{AcO} \\
\text{69\%}
\end{array}$$

Thus, we designed the more stable diene 35.

Monobenzylation of 1,3-propanediol gave alcohol 36 which was transformed to the bromide 37 in good yield. Alternatively, benzyl protection of the hydroxyl group on 3-bromo-
1-propanol directly led to 37. Lithium-halogen exchange of 37 followed by the addition of 2,4-hexadienal led to dienol 38 which was acetylated to provide 35.

\[
\text{HO-} \xrightleftharpoons{60\% \text{ NaH, DMF}}^\text{BnBr 65\%} \text{HO} \xrightarrow{60\% \text{ NaH, DMF}}^\text{BnBr 85\%} \text{HO-}
\]

\[
\text{Br-} \xrightarrow{60\% \text{ NaH, DMF}}^\text{BnBr 65\%} \text{Br-}
\]

The reaction of 35 and 4 in boiling acetonitrile did not occur.

To our delight, ZnCl₂ facilitated the cycloaddition albeit in modest yield. The isolated cycloadduct was the triol 39 as a result of deacetylation in the reaction medium. Catalytic hydrogenation not only reduced the double bond but also cleaved the benzyl group. The resulting tetrol was heated in DMF at 120-130 °C to give benzoxazole 40. To selectively oxidize the primary alcohol in the presence of secondary alcohol, 40 was treated with Fetizon's reagent. However, it did not work. Ruthenium catalyzed oxidation of 40 did not provide the desired lactone.
As a means to make the pseudopteroxazole system, we needed to convert triflate group in 8b to acetyl group.

To test the feasibility of this idea, 8b was subjected to the Cabri condition followed by acid hydrolysis of the resulting enol ether to give a product with the oxazole ring opened. Acid treatment of this product in boiling benzene recyclized the opened oxazole ring to provide 41. Methanolysis removed the acetyl group in 41 and tosylation of the resulting alcohol led to 42. Ketone 42 was treated with LDA or t-BuOK in THF at 0 °C to afford a unidentified product which was later assigned as 43.
In the meantime we obtained a crystal of 42. The crystal structure of 42 clearly showed that we chose the wrong regioisomer from the Diels-Alder reaction.

At this stage we went back to the other isomer. By following the same sequence as
described before, triflate 8a was converted to 44. A crystal of 44 proved the structure of 44 unambiguously.

Tosylation of 44 afforded 45. However, the reaction of 45 with the anion of sulfone 26 and subsequent treatment with Na(Hg) led to a complex mixture of products.

We also applied other approaches we used earlier in case of the wrong isomer 8b to the
desired isomer 8a. Thus, triflate 8a was subjected to Cabri conditions to give enol ether 46. Ester hydrolysis and subsequent tosylation of 46 provided 47.

\[
\begin{align*}
\text{Pd(OAc)}_2, \text{DPPP} & \quad \text{TEA}, \text{CH}_2=\text{CHO}n-\text{Bu} \\
\text{DMF, 67\%} & \\
\end{align*}
\]

However, exposure of 47 to SnCl\(_4\) did not deliver the cyclized product.

At this time, 46 was converted to 49. Unmasked alcohol via hydrolysis attacked the neighboring carbonyl group to form hemiketal 50.

Unfortunately, we were not able to convert 50 to the desired tosylate.
Nucleophilic substitution of tosyl group in 45 by cuprate reagents was not successful, either.

In the meantime, we tried to develop the general route to tricyclic core skeletons using a Diels-Alder cycloaddition of ortho-quinones\textsuperscript{18} intramolecularly.

Thus, Friedel-Crafts acetylation of catechol led to 51\textsuperscript{19} which was silylated with TBSCl.

Ketone 52 was reacted with 2,4-hexadienal in the presence of potassium tert-butoxide to
give β-hydroxy ketone 53. Protection of the alcohol in 53 as an acetate produced 54.
Deprotection of TBS groups in 53 or 54 under acidic or basic condition gave 55 or the retroaldol products.

To avoid the deprotection, 51 was directly treated with 4 equivalents of LDA and 4 equivalents of HMPA and subsequent addition of aldehyde to produce 56. However, oxidation of 56 failed to deliver the cyclized product.

As illustrated below, we also employed quinone methide chemistry to construct the
bicyclic structure. To this end, esterification of 4-hydroxymandelic acid was first carried out to give its methyl ester 57. However, the reaction of 57 with excess diene in the presence of catalytic amount of TFA or a stoichiometric amount of PCl₃ did not give the desired product.

Another intramolecular Diels-Alder reaction was also examined. Thus, reaction of the enolate of acetovanillone with 2,4-hexadienal gave aldol adduct 58. Exposure of 58 to Phl(OAc)₂ in MeOH did not provide the expected product. LAH reduction of 58 led to triol 59 albeit in low yield. However, subjection of 59 to the same condition for 58 failed to afford the desired product, either.
At this stage, we carried out intermolecular Diels-Alder reaction of methoxy-1,4-benzoquinone with diene 3 with a view to comparing the regioselectivity of this case with the one of formamido-1,4-benzoquinone case. Disappointingly, either thermal or TiCl₄ catalyzed reaction resulted in about the same ratio that we obtained from the study with formamido-1,4-benzoquinone 4.

We also came up with an idea that cycloaddition of 2,4-hexadienol with simple benzoquinone would lead to adduct without any regiochemical problems and that regioselective addition of methanol or amine equivalent to the quinone after the oxidation could give the required isomer for subsequent elaboration.

Toward this end, cycloadduct 63 was obtained by reacting the benzoquinone with 2,4-hexadienol in boiling benzene albeit in low yield. Silver oxide treatment of 63 afforded
benzoquinone 62.

Acid catalyzed methanol addition\textsuperscript{21} to 62 gave rise to a mixture of products. Although amino group introduction in benzoquinone moiety was realized by reaction of 62 with methoxylamine,\textsuperscript{22} the selectivity of addition was not high.

In conclusion, a direct route to the tricyclic core skeleton of the originally proposed structures of antitubercular benzoxazole alkaloids – pseudopteroxazole and seco-pseudopteroxazole was developed employing an intermolecular Diels-Alder reaction as a key step. In an attempt to directly introduce the alkyl side chain, several dienes were also examined. In addition, two intramolecular Diels-Alder approaches were investigated to construct the core framework as well as a number of other synthetic strategies towards this
family of natural products. The research results delineated above will be useful to the synthesis of these natural products although the elaboration of the tricyclic intermediates to the final molecules and stereochemistry adjustment remain to be accomplished.

**Experimental Section**

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane and benzene were distilled over calcium hydride. All experiments were performed under argon atmosphere unless otherwise noted. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or Bruker 400 MHz instrument. All chemical shifts are reported relative to CDCl$_3$ (7.26 ppm for $^1$H and 77.06 ppm for $^{13}$C), unless otherwise noted. Coupling constants ($J$) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer and low resolution mass spectra were performed with a Finnegan 4023 mass spectrometer. Standard grade silica gel (60 A, 32-63 µm) was used for a flash column chromatography.

**(2E,4E)-Hexa-2,4-dienyl acetate (3)**

To a suspension of LAH (3.95 g, 104.026 mmol) in Et$_2$O (200 mL) was dropwise added a solution of 2,4-hexadienal (10 g, 104.026 mmol) in Et$_2$O (50 mL) at 0 °C. After being stirred at 0 °C for 1 h, the mixture was quenched with H$_2$O (5 mL), 1N NaOH (5 mL), and H$_2$O (15 mL) at 0 °C. The mixture was filtered through Celite and rinsed with Et$_2$O. The filtrate was evaporated in vacuo to provide alcohol (10.2 g, 100%). 300 MHz $^1$H NMR (CDCl$_3$) δ 6.27-6.11 (1H, m), 6.11-5.95 (1H, m), 5.80-5.60 (2H, m), 4.18 and 4.11 (2H, d, $J=$
5.7 Hz), 1.85 (1H, br s), 1.74 (3H, d, J = 6.3 Hz).

To a solution of alcohol (10.2 g, 104.026 mmol) in CH₂Cl₂ (208 mL) were successively added pyridine (12.62 mL, 156.039 mmol), DMAP (1.27 g, 10.4 mmol), and Ac₂O (12.76 mL, 135.234 mmol) at 0 °C. After being stirred at rt overnight, the mixture was washed with 10% HCl, H₂O, saturated NaHCO₃ solution, and brine, successively. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo to give 3 (14.286 g, 98%). 300 MHz H NMR (CDCl₃) δ 6.24 (1H, dd, J = 15.3, 10.5 Hz), 6.12-5.97 (1H, m), 5.83-5.68 (1H, m), 5.68-5.54 (1H, m), 4.61 and 4.55 (2H, d, J = 6.6 Hz), 2.07 (3H, s), 1.76 (3H, d, J = 6.6 Hz).

N-(2,5-Dimethoxyphenyl)formamide (5)

A mixture of 96% HCO₂H (50 mL, 1.325 mol) and AC₂O (21.56 mL, 228.48 mmol) was heated at 50-60 °C for 10 min before being cooled down to rt. Then, 2,5-dimethoxyaniline (10 g, 65.28 mmol) was added in one portion at rt. After being stirred at rt for 10 min, the mixture was concentrated in vacuo. To this residue was added cold H₂O and NaHCO₃ to make the mixture basic. The resulting mixture was extracted with ethyl acetate two times. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo to give 5 (11.71 g, 99%). 300 MHz H NMR (CDCl₃) δ 8.45 (1H, d, J = 1.8 Hz), 8.08 (1H, d, J = 3.0 Hz), 7.80 (1H, br s), 6.80 (1H, d, J = 9.0 Hz), 6.61 (1H, dd, J = 9.0, 3.0 Hz), 3.85 (3H, s), 3.78 (3H, s).

Formamido-1,4-benzoquinone (4)

To a solution of 5 (2 g, 11.04 mmol) in CH₂Cl₂ (80 mL) was added BBr₃ (4.2 mL, 44.16 mmol) at −78 °C. After the dry ice/acetone bath was removed, the mixture was stirred at rt for 40 min. After being carefully poured into cold H₂O, the mixture was extracted with ethyl acetate five or six times. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo to give dihydroquinone. 300 MHz H NMR (acetone-d₆) δ 9.11 (1H, br s), 8.40 (2H, br
The resulting dihydroquinone (~1.43 g, 9.31 mmol) was dissolved in ethyl acetate (40 mL) and CH$_2$Cl$_2$ (40 mL). PhI(OAc)$_2$ (3.6 g, 11.18 mmol) was added to this solution at rt. After 5 min, the solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with H$_2$O and brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was suspended in Et$_2$O and filtered. The yellowish solid (1.38 g, 83%) was obtained. 300 MHz $^1$H NMR (acetone-$d_6$) δ 9.51 (1H, br s), 8.68 (1H, br s), 7.49 (1H, br s), 6.89 (1H, d, $J = 10.2$ Hz), 6.78 (1H, dd, $J = 10.2$, 2.4 Hz).

(1S, 4R)-6-Formylamino-4-methyl-5,8-dioxo-1,4,5,8-tetrahydronaphthalen-1-ylmethyl acetate (5a), (1R, 4S)-7-Formylamino-4-methyl-5,8-dioxo-1,4,5,8-tetrahydronaphthalen-1-ylmethyl acetate (5b), (1S, 4R)-6-Formylamino-5,8-dihydroxy-4-methyl-1,4-dihydronaphthalen-1-ylmethyl acetate (6a), and (1R, 4S)-7-Formylamino-5,8-dihydroxy-4-methyl-1,4-dihydronaphthalen-1-ylmethyl acetate (6b)

A mixture of 3 (3.78 g, 27 mmol) and 4 (3.4 g, 22.5 mmol) in CH$_3$CN (25 mL) and H$_2$O (5 mL) was stirred at rt overnight. Then, it was heated to reflux for another 24 h. After being concentrated in vacuo, the residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was used for the next step without further purification. For NMR data, the residue was purified by sgc (H:EA = 2:1 to 1:2) to give 5a/b (~1.147 g) first and 6a/b (~3.441 g) later. Combined yield: 70%

5a/b: 300 MHz $^1$H NMR (acetone-$d_6$) δ 9.52 (1H, br s), 8.67 (1H, br s), 7.44 (1H, br s), 5.97 (1H, ddd, $J = 9.9$, 4.5, 0.9 Hz), 5.79 (1H, dd, $J = 9.9$, 4.5 Hz), 4.27 (1H, dd, $J = 10.8$, 4.8 Hz),
4.23-4.10 (1H, m), 3.76-3.64 (1H, m), 3.47-3.31 (1H, m), 1.95 and 1.94 (3H, s), 1.27 and 1.23 (3H, d, $J = 6.9$ Hz).

**6a/b:** 300 MHz $^1$H NMR (acetone-$d_6$) δ 9.52 (1H, br s), 8.60-7.83 (3H, m), 6.86 (1H, s), 6.03 (1H, dd, $J = 9.9, 4.8$ Hz), 5.92 (1H, dd, $J = 9.9, 4.5$ Hz), 4.38 (1H, dd, $J = 9.9, 3.9$ Hz), 4.15-4.00 (1H, m), 4.00-3.80 (1H, m), 3.75-3.51 (1H, m), 1.98 and 1.96 (3H, s), 1.32 and 1.31 (3H, d, $J = 6.6$ Hz).

(6S, 9R)-5-Hydroxy-9-methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalen-6-ylmethyl acetate (7a) and (6S, 9R)-5-Hydroxy-6-methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalen-9-yl methyl acetate (7b)

To a solution of 5a/b and 6a/b (4.588 g, 15.75 mmol) in ethyl acetate was carefully added 10% Pd/C (450 mg) at rt. After being stirred under H$_2$ balloon pressure at rt for 9 h, the mixture was filtered through Celite and rinsed with ethyl acetate. The filtrate was evaporated in vacuo to give hydroquinone with the isolated double bond reduced. 300 MHz $^1$H NMR (acetone-$d_6$) δ 9.48 (1H, br s), 8.30-8.20 (1H, m), 8.20-7.90 (2H, br s), 6.85 (1H, s), 4.48-4.33 (1H, m), 4.28-4.10 (1H, m), 3.50-3.02 (2H, m), 2.02, 2.00 (3H, s), 1.96-1.50 (4H, m), 1.29 (3H, d, $J = 6.9$ Hz).

The resulting crude was diluted with benzene (50 mL) and ethyl acetate (10 mL). To this mixture was added PTSA-H$_2$O (300 mg, 1.58 mmol). Then, it was heated to reflux overnight. After the mixture was concentrated in vacuo, the residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 2:1 to 1:1) to give 7a/b (3.5 g, 82%). 300 MHz $^1$H NMR (CDCl$_3$) δ 8.05 (1H, s), 7.18 and 7.16 (1H, s), 4.80-4.03 (2H, m), 3.55-3.38 (1H, m), 3.38-3.02 (1H, m), 2.11 and 2.01 (3H, s), 2.15-1.52 (4H, m), 1.47 and 1.27 (3H, d, $J$
(6S, 9R)-9-Methyl-5-trifluoromethanesulfonyloxy-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalen-6-ylmethyl acetate (8a) and (6S, 9R)-6-Methyl-5-trifluoromethanesulfonyloxy-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalen-9-ylmethyl acetate (8b)

To a solution of 7a/b (2.4074 g, 8.873 mmol) in THF (30 mL) was added 60% NaH (461 mg, 11.53 mmol) at 0 °C. After 5 min, PhN(Tf)₂ (3.49 g, 9.76 mmol) was added at 0 °C in one portion. After being stirred at rt for 4 h, the mixture was quenched with H₂O at 0 °C. The mixture was extracted with ethyl acetate two times. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give 8a (~1.804 g) first and 8b (~1.203 g) later. Combined yield: 84%

8a: 300 MHz ¹H NMR (CDCl₃) δ 8.16 (1H, s), 7.63 (1H, s), 4.26 (1H, dd, J = 8.4, 6.9 Hz), 4.16 (1H, dd, J = 8.1, 3.6 Hz), 3.55-3.45 (1H, m), 3.33-3.20 (1H, m), 2.15-1.95 (2H, m), 2.03 (3H, s), 1.80-1.58 (2H, m), 1.51 (3H, d, J = 6.9 Hz); 75 MHz ¹³C NMR (CDCl₃) δ 170.9, 154.1, 148.3, 145.1, 139.0, 129.6, 127.7, 120.8, 116.6, 112.2, 111.3, 65.2, 33.0, 29.6, 26.5, 23.4, 21.1, 20.9.

8b: 300 MHz ¹H NMR (CDCl₃) δ 8.11 (1H, s), 7.61 (1H, s), 4.61 (1H, dd, J = 8.1, 2.7 Hz), 4.52 (1H, dd, J = 8.1, 4.8 Hz), 3.59-3.45 (1H, m), 3.36-3.26 (1H, m), 2.10-1.90 (2H, m), 1.96 (3H, s), 1.90-1.73 (2H, m), 1.30 (3H, d, J = 5.1 Hz); 75 MHz ¹³C NMR (CDCl₃) δ 171.1, 153.5, 147.9, 145.0, 138.0, 135.1, 123.3, 122.4, 120.2, 117.0, 111.9, 66.1, 34.2, 28.0, 27.9, 20.9, 20.8, 20.6.

(6S, 9R)-6-Methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalen-9-ylmethyl acetate (9)
To a solution of 8b (1.272 g, 3.154 mmol) in DMF (43 mL) were added Ph3P (41 mg, 0.158 mmol), Pd(OAc)2 (14 mg, 0.063 mmol), Et3N (1.35 mL, 9.65 mmol), and 96% HCO2H (238 µL, 6.308 mmol) at rt. After being stirred at 70 °C under argon for 7 days, the mixture was diluted with ethyl acetate and washed with H2O three times. The organic layer was dried over MgSO4, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 4:1) to afford 9 (704 mg, 87%). 300 MHz 1H NMR (CDCl3) δ 8.05 (1H, s), 7.58 (1H, d, J = 8.4 Hz), 7.26 (1H, d, J = 8.4 Hz), 4.52 (1H, dd, J = 11.1, 4.5 Hz), 4.31 (1H, dd, J = 10.8, 9.3 Hz), 3.65-3.50 (1H, m), 3.10-2.90 (1H, m), 2.05 (3H, s), 2.10-1.97 (1H, m), 1.97-1.80 (2H, m), 1.75-1.68 (1H, m), 1.35 (3H, d, J = 6.9 Hz); 75 MHz 13C NMR (CDCl3) δ 171.3, 152.2, 149.1, 141.2, 137.8, 124.9, 120.0, 118.7, 66.0, 33.6, 33.0, 28.0, 23.0, 22.8, 21.2.

(6S, 9R)-(6-Methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalen-9-yl)methanol (10)

To a solution of 9 (704 mg, 2.76 mmol) in MeOH (9.2 mL) was added K2CO3 (419 mg, 3.04 mmol) at rt. After being stirred at rt for 3 h, the mixture was concentrated in vacuo. The residue was diluted with CH2Cl2 and washed with brine. The organic layer was dried over MgSO4, filtered, and evaporated in vacuo to give 10 (588 mg, 100%). 300 MHz 1H NMR (CDCl3) δ 7.94 (1H, s), 7.53 (1H, d, J = 8.4 Hz), 7.25 (1H, d, J = 8.4 Hz), 4.05 (1H, dd, J = 10.8, 3.9 Hz), 3.92 (1H, dd, J = 10.5, 7.8 Hz), 3.45-3.30 (1H, m), 3.06-2.88 (1H, m), 2.58 (1H, br s), 2.27-2.05 (1H, m), 1.96-1.79 (2H, m), 1.79-1.60 (1H, m), 1.35 (3H, d, J = 7.2 Hz); 75 MHz 13C NMR (CDCl3) δ 152.0, 149.1, 141.6, 137.5, 125.0, 121.1, 118.2, 64.9, 37.1, 36.4, 33.1, 28.3, 22.9, 22.6.

1-Cyclohexyl-1-hydroxy-5-methy1hex-4-en-3-one (11)

To a solution of diisopropylamine (785 µL, 5.6 mmol) in THF (17 mL) was added n-
BuLi (2.5 M solution in hexanes, 2.24 mL, 5.6 mmol) at −78 °C. After 15 min at −78 °C, mesityl oxide (500 mg, 5.09 mmol) was slowly added at −78 °C. After 10 min at −78 °C, cyclohexanecarboxaldehyde (555 µL, 4.58 mmol) was dropwise added at −78 °C. After being gradually warmed up to rt, the mixture was quenched with H₂O. The mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give 11 (751 mg, 78%).

300 MHz ¹H NMR (CDCl₃) δ 6.06 (IH, s), 3.89-3.73 (IH, m), 2.62 (IH, dd, J = 17.4, 2.7 Hz), 2.49 (IH, dd, J = 17.1, 9.3 Hz), 2.15 (3H, s), 1.90 (3H, s), 1.92-0.90 (11H, m).

(1E)-1-Cyclohexyl-5-methylhexa-1,4-dien-3-one (12)

A mixture of 11 (149 mg, 0.71 mmol) and PTSA·H₂O (40.5 mg, 0.21 mmol) in benzene (3 mL) was stirred at rt for 7 h. The mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give 12 (135.6 mg, 99%).

300 MHz ¹H NMR (CDCl₃) δ 6.75 (IH, dd, 15.9, 6.6 Hz), 6.22 (IH, s), 6.07 (IH, dd, J = 15.9, 1.5 Hz), 2.42-2.05 (IH, m), 2.14 (3H, s), 1.91 (3H, s), 1.92-1.02 (10H, m).

[(1E/Z)-3-Cyclohexyl-1-(2-methylpropenyl)but-1-enyloxy]trimethylsilane (13)

To a suspension of CuCN (53 mg, 0.59 mmol) in THF (3 mL) was added MeLi (1.4 M solution in THF, 842 µL, 1.18 mmol) at 0 °C. After 5 min, TMSCl (75 µL, 0.59 mmol) was added to this mixture at 0 °C. After 5 min, a solution of 12 (103 mg, 0.536 mmol) in THF (1 mL + 1 mL for rinse) was transferred to this mixture at 0 °C via cannula. After being stirred at rt overnight, the mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 50:1) to give 13 (94 mg, 65%).

300 MHz ¹H NMR (CDCl₃) δ 5.72 and 5.51 (1H, s).
s), 4.55 and 4.40 (1H, d, J = 6.6 Hz), 2.40 and 2.05 (1H, m), 1.84 and 1.81 (3H, s), 1.76 and 1.75 (3H, s), 1.78-0.80 (11H, m), 0.92 and 0.91 (3H, d, J = 6.9 Hz), 0.18 and 0.15 (9H, s).

6-Cyclohexyl-2-methylhept-2-en-4-one (14)

To a solution of 13 (42 mg, 0.156 mmol) in THF (1 mL) was added TBAF (1 M solution in THF, 187 µL, 0.187 mmol) at rt. After 5 min, the mixture was concentrated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give 14 (32 mg, 98%). 300 MHz ¹H NMR (CDCl₃) δ 6.04 (1H, t, J = 1.2 Hz), 2.33 (1H, dd, J = 15.0, 4.8 Hz), 2.14 (1H, dd, J = 15.0, 9.0 Hz), 2.11 (3H, s), 1.86 (3H, s), 1.95-0.82 (12H, m), 0.81 (3H, d, J = 6.9 Hz).

(6S, 9R)-6-Methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalene-9-carbaldehyde (15)

1) from PCC oxidation:

To a solution of 10 (32.8 mg, 0.154 mmol) in CH₂Cl₂ (2 mL) were added Celite (36 mg) and PCC (36 mg, 0.169 mmol) at rt. After the mixture was stirred at rt for 1 h, more PCC (10 mg, 0.046 mmol) was added. After additional 1 h, the mixture was diluted with Et₂O, filtered through Celite, and rinsed with Et₂O. The filtrate was evaporated in vacuo. The residue was purified by sgc (H:EA = 4:1) to afford 15 (27.7 mg, 85%).

2) from Dess-Martin periodinane oxidation:

To a solution of 10 (45 mg, 0.211 mmol) in CH₂Cl₂ (2 mL) was added Dess-Martin periodinane (98 mg, 0.231 mmol) at rt. After being stirred at rt for 30 min, the mixture was diluted with Et₂O. The mixture was filtered through Celite and rinsed with Et₂O. The filtrate was evaporated in vacuo to give 15 (38 mg, 85%). 300 MHz ¹H NMR (CDCl₃) δ 9.83 (1H, s), 8.06 (1H, d, J = 8.4 Hz), 7.34 (1H, d, J = 8.4 Hz), 4.08-3.95 (1H, m), 3.15-2.93 (1H, m), 2.46-2.26 (1H, m), 2.26-1.76 (2H, m), 1.76-1.41 (1H, m), 1.34 (3H, d, J = 7.2 Hz).
1-Hydroxy-5-methyl-1-(6-methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]napthalen-9-yl)hex-4-en-3-one (16)

To a solution of diisopropylamine (13 μL, 0.095 mmol) in THF (1 mL) was added n-BuLi (2.5 M solution in hexanes, 38 μL, 0.095 mmol) at -78 °C. After 15 min at -78 °C, mesityl oxide (10 μL, 0.087 mmol) was slowly added at -78 °C. After 10 min at -78 °C, a solution of 15 (16.7 mg, 0.079 mmol) in THF (1 mL) was transferred to the mixture at -78 °C via cannula. After being gradually warmed up to rt, the mixture was quenched with H2O. The mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO4, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 5:1 to 2:1) to give 16 (14.5 mg, 59%). 300 MHz 1H NMR (CDCl3) δ 8.26-7.15 (3H, m), 6.12-5.86 (IH, m), 5.05-4.62 (2H, m), 3.60-1.15 (17H, m).

4-Methyl-1-(triphenyl-15-phosphanylidene)pent-3-en-2-one (17)

To a suspension of methyltriphenylphosphonium iodide (10 g, 24.74 mmol) in THF (60 mL) was added n-BuLi (2.5 M solution in hexanes, 9.9 mL, 24.74 mmol) at -78 °C. After being stirred at rt for 20 min, the mixture was recooled to -78 °C. Then, a solution of 3,3-dimethylacryloyl chloride (1.5 g, 12.65 mmol) in THF (15 mL) was added to this mixture at -78 °C via cannula. After being stirred at rt for 30 min, the mixture was quenched with H2O. The mixture was diluted with Et2O and washed with H2O and brine. The aqueous layer was extracted with Et2O two times more. The organic layer was dried over MgSO4, filtered, and evaporated in vacuo. The residue was triturated with solvent (H:EA = 10:3) and evaporated again to give the yellowish solid 17 (4.3 g, 96%). 300 MHz 1H NMR (CDCl3) δ 7.82-7.32 (15H, m), 6.03 (1H, s), 3.74 (1H, d, J = 26.1 Hz), 2.13 (3H, s), 1.79 (3H, s).

5-Methyl-1-(6-methyl-7,8-dihydro-6H-1-oxa-3-azacyclopenta[a]napthalen-9-
ylidene)hex-4-en-3-one (18)

A mixture of 15 (44.6 mg, 0.211 mmol) and 17 (361 mg, 1 mmol) in CH$_2$Cl$_2$ (2 mL) was heated to reflux for 5 h. The mixture was concentrated in vacuo and the residue was purified by sgc (H:EA = 10:1) to give 18 (37.9 mg, 61%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 8.11 (1H, s), 7.56 (1H, d, $J = 8.1$ Hz), 7.20 (1H, d, $J = 8.1$ Hz), 7.01 (1H, t, $J = 7.2$ Hz), 6.17 (1H, s), 3.44 (2H, d, $J = 7.2$ Hz), 3.15-3.00 (1H, m), 2.70-2.48 (2H, m), 2.18 (3H, s), 2.06-1.86 (1H, m), 1.90 (3H, s), 1.80-1.65 (1H, m), 1.30 (3H, d, $J = 6.9$ Hz); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 198.2, 156.6, 152.2, 147.9, 141.1, 138.9, 133.1, 125.0, 123.6, 122.4, 121.0, 118.8, 44.4, 33.9, 30.0, 28.0, 23.6, 22.1, 21.1.

5-Methyl-1-(6-methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalen-9-yl)hexa-1,4-dien-3-one (19)

A mixture of 15 (47.3 mg, 0.224 mmol) and 17 (241 mg, 0.672 mmol) in CH$_2$Cl$_2$ (2 mL) was stirred at rt overnight. The solvent was evaporated in vacuo and the residue was purified by sgc (H:EA = 10:1) to give 19 (34.5 mg, 52%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 8.15-6.85 (4H, m), 6.21-5.85 (2H, m), 4.15-4.00 (1H, m), 3.20-2.93 (1H, m), 2.40-1.20 (13H, m).

(6S, 9R)-6-Methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalen-9-ylmethyl toluene-4-sulfonate (20)

To a solution of 10 (43 mg, 0.202 mmol) in CH$_2$Cl$_2$ (2 mL) were added pyridine (25 µL, 0.303 mmol) and TsCl (42 mg, 0.222 mmol) at 0 °C. After being stirred at rt overnight, the mixture was concentrated in vacuo. The residue was diluted with ethyl acetate and washed with 10% HCl, saturated NaHCO$_3$ solution, and brine, successively. The organic layer was dried over MgSO$_4$, filtered, evaporated in vacuo. The residue was purified by sgc (H:EA = 2:1) to give 20 (69 mg, 93%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.89 (1H, s), 7.65 (2H, d, $J = 8.1$ Hz),...
(6S,9R)-9-Iodomethyl-6-methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalene (21)

A mixture of 20 (296 mg, 0.806 mmol) and NaI (157 mg, 1.05 mmol) in acetone (3 mL) was heated to reflux for 4 h. After the mixture was concentrated in vacuo, the residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 4:1) to afford 21 (250 mg, 95%). 300 MHz ¹H NMR (CDCl₃) δ 8.05 (1H, s), 7.60 (1H, d, J = 8.4 Hz), 7.22 (1H, d, J = 8.4 Hz), 3.76 (1H, dd, J = 9.6, 3.0 Hz), 3.59 (1H, dd, J = 9.6, 9.6 Hz), 3.45-3.32 (1H, m), 3.05-2.88 (1H, m), 2.22-2.05 (1H, m), 2.05-1.80 (2H, m), 1.70-1.53 (1H, m), 1.36 (3H, d, J = 7.2 Hz); 75 MHz ¹³C NMR (CDCl₃) δ 152.1, 149.0, 140.8, 138.1, 125.2, 122.0, 119.0, 36.3, 33.3, 27.9, 25.9, 23.0, 12.3.

(6S,9R)-6,9-Dimethyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalene (22)

To a solution of t-BuLi (1.7 M solution in pentane, 88 µL, 0.15 mmol) in THF (1 mL) was slowly added a solution of 21 (24.5 mg, 0.075 mmol) in THF (1 mL) at −78 °C. After 5 min, a solution of 5-bromo-2-methyl-2-pentene (12.2 mg, 0.075 mmol) in THF (0.5 mL) was added to this mixture at −78 °C. After being stirred at −78 °C for 10 min, the mixture was quenched with H₂O at −78 °C, diluted with ethyl acetate, and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by
sgc (H:EA = 50:1) to give 22 (9.8 mg, 65%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 8.05 (1H, s), 7.54 (1H, d, $J$ = 8.1 Hz), 7.25 (1H, d, $J$ = 8.1 Hz), 3.40-3.25 (1H, m), 3.06-2.88 (1H, m), 2.02-1.79 (2H, m), 1.79-1.56 (2H, m), 1.43 (3H, d, $J$ = 7.2 Hz), 1.36 (3H, d, $J$ = 7.2 Hz).

6-Methyl-9-methylene-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalene (23)

1) from the reaction with allyltributyltin:

To a solution of 21 (15.7 mg, 0.048 mmol) in toluene (2 mL) were added allyltributyltin (30 $\mu$L, 0.096 mmol) and AIBN (1.2 mg, 0.007 mmol) at rt. After being heated at 80 °C overnight, the mixture was evaporated in vacuo and the residue was purified by sgc (H:EA = 10:1) to afford 23 (4.8 mg, 50%).

2) from the reaction with KCN:

To a solution of 21 (57 mg, 0.174 mmol) in CH$_3$CN (1 mL) and H$_2$O (1 mL) were added KCN (23 mg, 0.348 mmol) and 18-crown-6 (5 mg, 0.017 mmol) at rt. After being stirred at rt overnight, the mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give 23 (22 mg, 64%).

3) from the reaction with PhSO$_2$Na:

A mixture of 21 (85 mg, 0.26 mmol) and PhSO$_2$Na (85 mg, 0.52 mmol) in DMF (1 mL) was stirred at rt overnight. The mixture was diluted with ethyl acetate and washed with H$_2$O three times. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give 23 (32 mg, 62%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 8.11 (1H, s), 7.61 (1H, d, $J$ = 8.1 Hz), 7.25 (1H, d, $J$ = 8.1 Hz), 6.17 (1H, s), 5.37 (1H, s), 3.22-3.05 (1H, m), 2.80-2.64 (1H, m), 2.60-2.46 (1H, m), 2.14-1.96 (1H, m), 1.82-1.66 (1H, m), 1.35 (3H, d, $J$ = 6.9 Hz); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 152.3, 148.1, 141.2,
(6S, 9R)-6-Methyl-9-phenylthiomethyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalene (24)

To a solution of PhSH (96 µL, 0.935 mmol) in THF (2 mL) was added 60% NaH (37 mg, 0.935 mmol) at 0 °C. After 10 min, a solution of 21 (61 mg, 0.187 mmol) in THF (1 mL) was added to this mixture at 0 °C. After being stirred at rt for 30 min, the mixture was quenched with saturated NH₄Cl, diluted with ethyl acetate, and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give 24 (45 mg, 76%). 300 MHz ¹H NMR (CDCl₃) δ 8.01 (1H, s), 7.58 (1H, d, J = 8.1 Hz), 7.49-7.37 (2H, m), 7.37-7.11 (4H, m), 3.67 (1H, dd, J = 12.9, 3.0 Hz), 3.55-3.40 (1H, m), 3.12 (1H, dd, J = 12.9, 10.5 Hz), 3.06-2.89 (1H, m), 2.35-2.18 (1H, m), 1.99-1.80 (2H, m), 1.73-1.57 (1H, m), 1.39 (3H, d, J = 6.9 Hz).

(6S, 9R)-9-Benzenesulfinylmethyl-6-methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalene (25)

To a solution of 24 (45 mg, 0.146 mmol) in THF (1 mL) and H₂O (1 mL) was added NaIO₄ (62 mg, 0.292 mmol) at rt. After 4 h at rt, more NaIO₄ (62 mg, 0.292 mmol) was added and stirred at rt for another 5 h. The mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 2:1 to 1:1) to give 25 (20 mg, 43%). 300 MHz ¹H NMR (CDCl₃) δ 8.06-7.21 (8H, m), 3.99-2.88 (4H, m), 2.40-1.50 (4H, m), 1.40 and 1.36 (3H, d, J = 6.9 Hz).

(4-Methyl-3-pentenyl)phenylsulfone (26)

A mixture of 5-bromo-2-methyl-2-pentene (1.7 g, 10.4 mmol) and PhSO₂Na (2.05 g,
12.48 mmol) in DMF (10 mL) was stirred at rt overnight. Then, the mixture was diluted with ethyl acetate and washed with H$_2$O three times. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1 to 5:1) to give 26 (1.4 g, 60%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.96-7.85 (2H, m), 7.70-7.60 (1H, m), 7.60-7.50 (2H, m), 4.95 (1H, t, $J$ = 7.2 Hz), 3.14-3.01 (2H, m), 2.38 (2H, q, $J$ = 7.5 Hz), 1.61 (3H, s), 1.53 (3H, s).

9-(2-Benzencesulfonyl-5-methylhex-4-enyl)-6-methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalene (27)

To a solution of 26 (101 mg, 0.45 mmol) in THF (1 mL) was added n-BuLi (2.5 M solution in hexanes, 150 $\mu$L, 0.375 mmol) at -78 °C. After 10 min, a solution of 21 (49 mg, 0.15 mmol) in THF (1 mL) was dropwise added to this mixture at -78 °C. After being stirred at -78 °C for 20 min, the mixture was quenched with H$_2$O, diluted with ethyl acetate, and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 5:1 to 2:1) to give 27 (44 mg, 70%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 8.10-6.72 (8H, m), 5.10-4.70 (1H, m), 3.40-1.10 (20H, m).

6-Hydroxy-2-methylundeca-2,7,9-trien-4-one (29)

To a solution of diisopropylamine (1.57 mL, 11.2 mmol) in THF (30 mL) was slowly added n-BuLi (2.5 M solution in hexanes, 4.48 mL, 11.2 mmol) at -78 °C. After 20 min, mesityl oxide (1 g, 10.188 mmol) was dropwise added to this mixture at -78 °C. After 20 min, a solution of 2,4-hexadienal (1.124 mL, 10.188 mmol) in THF (4 mL) was slowly added to this mixture at -78 °C. After being slowly warmed up to -40 ~ -50 °C, the mixture was quenched with AcOH (642 $\mu$L, 11.2 mmol) in THF (3 mL). The mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and
evaporated in vacuo. The residue was purified by sgc (H:EA = 6:1) to give 29 (1.29 g, 65%).

300 MHz $^1$H NMR (CDCl$_3$) δ 6.23 (1H, dd, $J$ = 15.3, 10.5 Hz), 6.10-5.92 (2H, m), 5.79 (1H, dd, $J$ = 15.0, 6.9 Hz), 5.55 (1H, dd, $J$ = 15.3, 6.9 Hz), 4.67-4.52 (1H, m), 3.36 (1H, br s), 2.74-2.55 (2H, m), 2.15 (3H, s), 1.89 (3H, s), 1.73 (3H, d, $J$ = 6.6 Hz).

1-(4-Methyl-2-oxopent-3-enyl)hexa-2,4-dienyl acetate (28)

To a solution of 29 (1.1864 g, 6.11 mmol) in CH$_2$Cl$_2$ (12 mL) were added DMAP (1.12 g, 9.165 mmol) and Ac$_2$O (691 µL, 7.332 mmol) at 0 °C. After being stirred at rt for 4 h, the mixture was concentrated in vacuo. The residue was diluted with ethyl acetate and washed with 10% HCl, saturated NaHCO$_3$ solution, and brine, successively. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1 to 5:1) to give 28 (1.324 g, 92%). 300 MHz $^1$H NMR (CDCl$_3$) δ 6.23 (1H, dd, $J$ = 15.3, 10.5 Hz), 6.09-5.90 (2H, m), 5.80-5.61 (2H, m), 5.50 (1H, dd, $J$ = 15.3, 6.9 Hz), 2.81 (1H, dd, $J$ = 15.6, 7.8 Hz), 2.63 (1H, dd, $J$ = 15.6, 5.7 Hz), 2.11 (3H, s), 2.00 (3H, s), 1.88 (3H, s), 1.73 (3H, d, $J$ = 6.6 Hz).

Methoxycarbonyl-1,4-benzoquinone (30)

A mixture of 2,5-dihydroxybenzoic acid (5.24 g, 34 mmol) and c-H$_2$SO$_4$ (0.5 mL) in MeOH (100 mL) was heated to reflux overnight with the occasional removal of H$_2$O and MeOH (Dean-Stark trap was used). After the solvent was evaporated in vacuo, the residue was diluted with ethyl acetate and washed with saturated NaHCO$_3$ solution. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo to give methyl ester (5.72 g, 100%) as a white solid. 300 MHz $^1$H NMR (CDCl$_3$) δ 10.3 (1H, s), 7.27 (1H, d, $J$ = 3.3 Hz), 7.01 (1H, dd, $J$ = 8.7, 3.3 Hz), 6.88 (1H, d, $J$ = 8.7 Hz), 4.52 (2H, br s), 3.93 (3H, s).

To a solution of dihydroquinone (3.1 g, 18.44 mmol) in benzene (184 mL) were added
Na$_2$SO$_4$ (5.5 g, 38.72 mmol) and Ag$_2$O (8.55 g, 36.88 mmol) at rt. The reaction flask was covered with aluminum foil. After being stirred at rt overnight, the mixture was filtered through Celite, rinsed with ethyl acetate, and the filtrate was evaporated in vacuo to give benzoquinone 30 (3.06 g, 100%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.07 (1H, s), 6.80 (2H, s), 3.87 (3H, s).

**Methyl 1-(1-acetoxy-5-methyl-3-oxohex-4-enyl)-4,8a-dimethyl-5,8-dioxo-1,3,4,5,8,8a-hexahydro-2H-naphthalene-4a-carboxylate (31)**

A mixture of 28 (273 mg, 1.156 mmol) and 30 (160 mg, 0.963 mmol) in CH$_3$CN (3.2 mL) was heated to reflux overnight. After the solvent was evaporated in vacuo, the residue was purified by sgc (H:EA = 3:1 to 1:1) to give 31 (252 mg, 65%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 6.79 (1H, d, $J$ = 10.5 Hz), 6.65 (1H, d, $J$ = 10.5 Hz), 6.11 (1H, s), 5.80-5.51 (3H, m), 4.05 (1H, d, $J$ = 4.8 Hz), 3.80 (3H, s), 3.35-3.20 (1H, m), 3.01 (1H, dd, $J$ = 15.6, 3.9 Hz), 2.67 (1H, dd, $J$ = 15.6, 7.2 Hz), 2.47-2.32 (1H, m), 2.13 (3H, s), 1.95 (3H, s), 1.90 (3H, s), 0.88 (3H, d, $J$ = 6.9 Hz).

**((4-Methoxybenzyl)propargylether (33)**

To a suspension of 60% NaH (1.74 g, 43.44 mmol) in THF (70 mL) was slowly added a solution of p-methoxybenzyl alcohol (5 g, 36.2 mmol) in THF (5 mL) at 0 °C. After being stirred at for 30 min, the mixture was recooled down to 0 °C. Then, a solution of propargyl bromide (80% in toluene, 4.84 mL, 43.44 mmol) in THF (5 mL) was added to this mixture at 0 °C. After being stirred at rt for 4 h, the mixture was quenched with saturated NH$_4$Cl. After the solvent was evaporated in vacuo, the residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 20:1) to afford 33 (5.85 g, 92%). 300 MHz $^1$H NMR
(CDCl₃) δ 7.29 (2H, d, J = 8.7 Hz), 6.88 (2H, d, J = 8.7 Hz), 4.55 (2H, s), 4.14 (2H, d, J = 2.4 Hz), 3.81 (3H, s), 2.46 (1H, t, J = 2.4 Hz).

1-(4-Methoxybenzyloxy)nona-5,7-dien-2-yn-4-ol (34)

To a solution of 33 (4.584 g, 26.05 mmol) in THF (56 mL) was slowly added n-BuLi (2.5 M solution in hexanes, 10.4 mL, 26.05 mmol) at -78 °C. After 10 min, a solution of 2,4-hexadienal (2.9 mL, 26.05 mmol) in THF (10 mL) was added to this mixture at -78 °C. After being stirred at -78 °C for 10 min, the mixture was quenched with saturated NH₄Cl. After the solvent was evaporated in vacuo, the residue was purified by sgc (H:EA = 5:1 to 2:1) to provide 34 (6.735 g, 95%). 300 MHz ¹H NMR (CDCl₃) δ 7.28 (2H, d, J = 8.7 Hz), 6.88 (2H, d, J = 8.7 Hz), 6.37 (1H, dd, J = 15.3, 10.5 Hz), 6.06 (1H, dd, J = 15.3, 10.5 Hz), 5.87-5.72 (1H, m), 5.65 (1H, dd, J = 15.3, 6.9 Hz), 4.96 (1H, t, J = 6.9 Hz), 4.53 (2H, s), 4.20 (2H, d, J = 1.8 Hz), 3.80 (3H, s), 2.00 (1H, d, J = 6.9 Hz), 1.77 (3H, d, J = 6.9 Hz).

1-[3-(4-Methoxybenzyloxy)prop-1-ynyl]hexa-2,4-dienyl acetate (32)

To a solution of 34 (1.325 g, 4.87 mmol) in CH₂Cl₂ (9.7 mL) were added pyridine (591 µL, 7.31 mmol), DMAP (59 mg, 0.49 mmol), and Ac₂O (597 µL, 6.33 mmol) at 0 °C. After being stirred at rt for 5 h, the mixture was diluted with CH₂Cl₂ and washed with 10% HCl, saturated NaHCO₃ solution, and brine, successively. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 5:1) to give 32 (1.056 g, 69%). 300 MHz ¹H NMR (CDCl₃) δ 7.28 (2H, d, J = 8.7 Hz), 6.87 (2H, d, J = 8.7 Hz), 6.46 (1H, dd, J = 15.3, 10.5 Hz), 6.06 (1H, dd, J = 15.3, 10.6 Hz), 5.96 (1H, d, J = 6.9 Hz), 5.90-5.73 (1H, m), 5.60 (1H, dd, J = 15.3, 6.9 Hz), 4.53 (2H, s), 4.19 (2H, d, J = 1.8 Hz), 3.80 (3H, s), 2.09 (3H, s), 1.78 (3H, d, J = 6.9 Hz).

3-Benzylloxypopropan-1-ol (36)
To a solution of 1,3-propanediol (1 g, 13.14 mmol) in DMF (20 mL) was added 60% NaH (631 mg, 15.77 mmol) at 0 °C. After being stirred at rt for 30 min, a solution of benzyl bromide (1.41 mL, 11.83 mmol) in DMF (5 mL) was slowly added to this mixture at 0 °C. After being stirred at rt overnight, the mixture was quenched with H₂O, diluted with ethyl acetate, and washed with H₂O three times. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give 36 (1.276 g, 65%). 300 MHz ¹H NMR (CDCl₃) δ 7.40-7.23 (5H, m), 4.53 (2H, s), 3.79 (2H, t, J= 5.7 Hz), 3.67 (2H, t, J= 5.7 Hz), 2.23 (1H, br s), 1.95-1.81 (2H, m).

3-Benzylxypropyl bromide (37)

1) from 36:

To a solution of 36 (980 mg, 5.9 mmol) in CH₂Cl₂ (12 mL) were added Ph₃P (1.7 g, 6.49 mmol) and CBr₄ (2.15 g, 6.49 mmol) at 0 °C. After being stirred at rt for 10 min, the solvent was evaporated in vacuo and the residue was purified by sgc (H:EA = 20:1) to give 37 (1.35 g, 100%).

2) from 3-bromo-1-propanol:

To a vigorously stirred mixture of 60% NaH (3.72 g, 92.88 mmol) and benzyl bromide (8.6 mL, 72 mmol) in DMF (304 mL) was dropwise added 3-bromo-1-propanol (10 g, 72 mmol) at -78 °C over 30 min. Then, dry ice/acetone bath was removed and the mixture was stirred at rt overnight. The mixture was quenched with H₂O, diluted with n-hexane, and washed with H₂O three times. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 30:1) to give 37 (14.015 g, 85%). 300 MHz ¹H NMR (CDCl₃) δ 7.43-7.23 (5H, m), 4.53 (2H, s), 3.61 (2H, t, J= 5.7 Hz), 3.54 (2H, t, J= 5.7 Hz), 2.23-2.10 (2H, m).
**1-Benzylxynona-5,7-dien-4-ol (38)**

To a solution of 37 (522 mg, 2.28 mmol) in Et$_2$O (12 mL) was slowly added t-BuLi (1.7 M solution in pentane, 2.7 mL, 4.56 mmol) at -78 °C. After 20 min, a solution of 2,4-hexadienal (252 µL, 2.28 mmol) in Et$_2$O (9 mL) was slowly added to this mixture at -78 °C. After being stirred at -78 °C for 15 min, the mixture was quenched with saturated NH$_4$Cl at -78 °C. The mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 5:1) to give 38 (492 mg, 88%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.45-7.23 (5H, m), 6.17 (1H, dd, $J = 15.6, 10.5$ Hz), 6.02 (1H, dd, $J = 15.6, 10.5$ Hz), 5.77-5.62 (1H, m), 5.56 (1H, dd, $J = 15.0, 6.6$ Hz), 4.51 (2H, s), 4.14 (1H, q, $J = 6.3$ Hz), 3.60-3.43 (2H, m), 2.18 (1H, br s), 1.75 (3H, d, $J = 6.6$ Hz), 1.80-1.50 (4H, m).

**1-(3-BenzylxoxpropyI)hexa-2,4-dienyl acetate (35)**

To a solution of 38 (492 mg, 2 mmol) in Et$_2$O were added DMAP (269 mg, 2.2 mmol) and Ac$_2$O (208 µL, 2.2 mmol) at rt. After being stirred at rt for 10 min, the mixture was diluted with ethyl acetate and washed with 10% HCl, saturated NaHCO$_3$ solution, and brine, successively. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give 35 (508 mg, 88%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.40-7.23 (5H, m), 6.20 (1H, dd, $J = 15.6, 10.5$ Hz), 6.00 (1H, dd, $J = 15.6, 10.5$ Hz), 5.81-5.64 (1H, m), 5.45 (1H, dd, $J = 15.0, 6.6$ Hz), 5.25 (1H, q, $J = 6.3$ Hz), 4.49 (2H, s), 3.47 (2H, t, $J = 6.3$ Hz), 2.03 (3H, s), 1.75 (3H, d, $J = 6.9$ Hz), 1.80-1.51 (4H, m).

**N-[5-(4-Benzylxox-1-hydroxybutyl)-1,4-dihydroxy-8-methyl-5,6,7,8-tetrahydroanaphthalen-2-yl]formamide (39)**

To a solution of 4 (500 mg, 3.31 mmol) in THF (10 mL) was added ZnCl$_2$ (496 mg, 3.64
mmol) at 0 °C. After being stirred at 0 °C for 30 min, a solution of 35 (1.14 g, 3.97 mmol) in THF (2 mL + 2 mL for rinse) was added to this mixture at 0 °C. After the mixture was stirred at rt for 4 days, more ZnCl₂ (496 mg, 3.64 mmol) was added to this mixture at rt and the mixture was stirred at rt for another 7 days. After the solvent was evaporated in vacuo, the residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1 to 5:1) to give 39 (592 mg, 45%). 300 MHz ¹H NMR (CDCl₃) δ 8.59 (1H, br s), 8.12 (1H, br s), 7.53 (1H, br s), 7.42-7.20 (5H, m), 6.58-6.50 (1H, m), 6.15-5.90 (2H, m), 5.71-5.31 (2H, m), 4.55-4.42 (2H, m), 3.78-3.35 (2H, m), 2.25-2.06 (1H, m), 1.80-1.40 (4H, m), 1.24 (3H, d, J = 6.9 Hz).

1-(5-Hydroxy-9-methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalen-6-yl)butane-1,4-diol (40)

To a solution of 39 (145 mg, 0.365 mmol) in ethyl acetate (5 mL) was carefully added 10% Pd/C (39 mg) at rt. After being stirred under H₂ balloon pressure at rt overnight, the mixture was filtered through Celite and rinsed with ethyl acetate. The filtrate was evaporated in vacuo to give debenzylated product with the double bond reduced (113 mg, 100%). 300 MHz ¹H NMR (acetone-d₆) δ 9.08 (1H, br s), 8.33 (2H, br s), 7.80 (1H, br s), 7.43 (1H, s), 6.80-6.62 (1H, m), 3.80-3.40 (3H, m), 3.23-2.95 (2H, m), 1.90-0.70 (11H, m).

A solution of reduced product (101 mg, 0.327 mmol) in DMF (2 mL) was heated at 120 ~ 130 °C overnight. After the solvent was removed by evaporation, the residue was purified by sgc (H:EA = 2:1) to give 40 (49 mg, 52%). 300 MHz ¹H NMR (CDCl₃) δ 8.59 (1H, br s), 8.35 (1H, br s), 7.53 (1H, br s), 6.60-6.45 (1H, m), 3.75-3.50 (3H, m), 3.03-2.80 (2H, m), 1.95-0.70 (11H, m).
5-Acetyl-6-methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclo[α]naphthalen-9-ylmethyl acetate (41)

To a solution of \( 8b \) (341 mg, 0.845 mmol) in DMF (2.3 mL) were added \( \text{Et}_3\text{N} \) (236 μL, 1.69 mmol), \( n \)-butyl vinyl ether (547 μL, 4.23 mmol), DPPP (19 mg, 0.046 mmol), and \( \text{Pd(OAc)}_2 \) (9.5 mg, 0.042 mmol) at rt. After being purged with argon for 5 min, the mixture was stirred at 80 °C for 6 h. After the mixture was cooled down to 0 °C, 10% HCl (3.5 mL) was added at 0 °C. After being stirred at rt for 30 min, the mixture was diluted with ethyl acetate and washed with \( \text{H}_2\text{O} \) three times. The organic layer was dried over \( \text{MgSO}_4 \), filtered, and evaporated in vacuo. The residue was diluted in benzene (10 mL). PTSA-\( \text{H}_2\text{O} \) (16 mg, 0.08 mmol) was added and the mixture was heated to reflux for 6 h. After the solvent was evaporated in vacuo, the residue was diluted with ethyl acetate and washed with \( \text{H}_2\text{O} \). The organic layer was dried over \( \text{MgSO}_4 \), filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1) to give 41 (142 mg, 56%). 300 MHz \(^1\text{H} \) NMR (CDCl\(_3\)) \( \delta \) 8.10 (1H, s), 7.86 (1H, s), 4.56 (1H, dd, \( J = 10.8, 3.9 \) Hz), 4.44 (1H, dd, \( J = 10.8, 7.2 \) Hz), 3.77-3.64 (1H, m), 3.64-3.50 (1H, m), 2.62 (3H, s), 1.98 (3H, s), 2.06-1.90 (2H, m), 1.85-1.68 (2H, m), 1.22 (3H, d, \( J = 6.9 \) Hz).

5-Acetyl-6-methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclo[α]naphthalen-9-ylmethyl toluene-4-sulfonate (42)

To a solution of 41 (68 mg, 0.226 mmol) in MeOH (2 mL) was added \( \text{K}_2\text{CO}_3 \) (34 mg, 0.249 mmol) at rt. After being stirred at rt for 1 h, the mixture was concentrated in vacuo. The residue was diluted with \( \text{CH}_2\text{Cl}_2 \) and washed with brine. The organic layer was dried over \( \text{MgSO}_4 \), filtered, and evaporated in vacuo to give alcohol (58.4 mg, 100%). 300 MHz \(^1\text{H} \) NMR (CDCl\(_3\)) \( \delta \) 7.99 (1H, s), 7.75 (1H, s), 4.10 (1H, dd, \( J = 11.1, 6.6 \) Hz), 4.03 (1H, dd, \( J = \)
10.8, 3.6 Hz), 3.70-3.56 (1H, m), 3.50-3.35 (1H, m), 2.60 (3H, s), 2.22-2.02 (1H, m), 2.02-1.86 (1H, m), 1.85-1.68 (2H, m), 1.25 (3H, d, J = 6.9 Hz); 75 MHz $^1$C NMR (CDCl$_3$) $\delta$ 203.2, 152.9, 150.5, 142.5, 137.0, 136.8, 122.6, 118.8, 65.4, 37.4, 31.2, 29.3, 28.8, 23.0, 20.7.

To a solution of alcohol (58.4 mg, 0.225 mmol) in CH$_2$Cl$_2$ (2 mL) were added DMAP (41 mg, 0.338 mmol) and TsCl (51 mg, 0.27 mmol) at rt. After being stirred at rt overnight, the mixture was diluted with CH$_2$Cl$_2$ and washed with 10% HCl, saturated NaHCO$_3$ solution, and brine, successively. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 2:1) to give 42 (85.7 mg, 92%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.90 (1H, s), 7.80 (1H, s), 7.54 (2H, d, J = 8.4 Hz), 7.17 (2H, d, J = 8.4 Hz), 4.58-4.42 (2H, m), 3.72-3.65 (1H, m), 3.59-3.45 (1H, m), 2.61 (3H, s), 2.40 (3H, s), 2.10-1.80 (2H, m), 1.78-1.63 (2H, m), 1.19 (3H, d, J = 6.9 Hz).

To a solution of 42 (15.6 mg, 0.038 mmol) in THF (1 mL) was added t-BuOK (4.7 mg, 0.042 mmol) at 0 °C. After being stirred at 0 °C for 1 h, the mixture was quenched with saturated NH$_4$Cl, diluted with ethyl acetate, and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 5:1) to give 43 (7.3 mg, 80%). Alternatively, 42 was treated with LDA at 0 °C to provide 43. 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.64 (1H, s), 4.99 (1H, t, J = 8.7 Hz), 4.21 (1H, dd, J = 12.6, 8.4 Hz), 4.00-3.86 (1H, m), 3.50-3.31 (1H, m), 2.54 (3H, s), 2.07-1.45 (4H, m), 1.06 (3H, d, J = 6.9 Hz); 75 MHz $^1$C NMR (CDCl$_3$) $\delta$ 197.7, 167.8, 156.8, 144.4, 131.4, 130.6, 129.6, 81.7, 40.3, 30.8, 29.2, 29.1, 23.9, 20.7.

(9-Methyl-6,7,8,9-tetrahydro-1-oxa-3-azaenapta[a]naphthalen-6-yl)methanol (44)
The same procedures for 9 and 10 were applied.

**Acetate:** 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 8.05 (1H, s), 7.54 (1H, d, $J$ = 8.1 Hz), 7.24 (1H, d, $J$ = 8.1 Hz), 4.35 (1H, dd, $J$ = 11.1, 5.1 Hz), 4.23 (1H, dd, $J$ = 10.5, 8.4 Hz), 3.36-3.12 (2H, m), 2.06 (3H, s), 2.02-1.60 (4H, m), 1.44 (3H, d, $J$ = 6.9 Hz); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 171.3, 152.3, 149.2, 138.6, 134.2, 127.3, 125.6, 117.9, 68.1, 37.7, 29.0, 27.8, 23.3, 21.24, 21.2.

**44:** 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 8.00 (1H, s), 7.44 (1H, d, $J$ = 8.4 Hz), 7.20 (1H, d, $J$ = 8.4 Hz), 3.93-3.72 (2H, m), 3.30-3.12 (1H, m), 3.08-2.93 (1H, m), 2.10-1.94 (1H, m), 1.94-1.71 (2H, m), 1.71-1.55 (1H, m), 1.36 (3H, d, $J$ = 6.9 Hz); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 152.3, 149.2, 137.9, 135.4, 127.4, 125.6, 117.5, 66.7, 40.9, 28.9, 28.0, 22.8, 21.3.

**9-Methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalene-6-ylmethyl toluene-4-sulfonate (45)**

The same procedure for 20 was applied. 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 8.09 (1H, s), 7.75 (2H, d, $J$ = 8.4 Hz), 7.50 (1H, d, $J$ = 8.4 Hz), 7.30 (2H, d, $J$ = 8.4 Hz), 7.06 (1H, d, $J$ = 8.4 Hz), 4.27 (1H, dd, $J$ = 9.9, 4.8 Hz), 4.15 (1H, dd, $J$ = 9.9, 8.7 Hz), 3.33-3.17 (2H, m), 2.44 (3H, s), 2.05-1.75 (3H, m), 1.65-1.47 (1H, m), 1.39 (3H, d, $J$ = 6.9 Hz); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 152.5, 149.2, 145.1, 138.9, 133.1, 132.6, 130.1, 128.1, 127.5, 125.6, 118.1, 73.4, 37.9, 28.9, 27.5, 22.8, 21.9, 21.2.

**5-(1-Butoxyvinyl)-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalene-6-ylmethyl acetate (46)**

To a solution of 8a (2.854 g, 7.075 mmol) in DMF (21 mL) were added TEA (2 mL, 14.15 mmol), $n$-butyl vinyl ether (4.6 mL, 35.375 mmol), DPPP (160 mg, 0.389 mmol), and Pd(OAc)$_2$ (79 mg, 0.354 mmol) at rt. After being purged with argon for 5 min, the mixture was stirred at 80 °C for 3 h. After being cooled down to rt, the mixture was diluted with ethyl
acetate and washed with H$_2$O three times. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 20:1 to 10:1) to give 46 (1.704 g, 67%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 8.07 (1H, s), 7.57 (1H, s), 4.46-4.33 (2H, m), 4.23-4.10 (2H, m), 3.92-3.78 (2H, m), 3.72-3.60 (1H, m), 3.36-3.20 (1H, m), 2.06 (3H, s), 2.10-1.93 (2H, m), 1.80-1.60 (4H, m), 1.49 (3H, d, $J$ = 6.9 Hz), 1.54-1.34 (2H, m), 0.92 (3H, t, $J$ = 7.5 Hz); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 171.1, 162.2, 152.6, 149.5, 138.2, 136.1, 133.1, 127.3, 120.1, 86.9, 68.0, 66.2, 34.6, 31.2, 29.4, 26.5, 23.6, 22.0, 21.2, 19.6, 14.0.

5-(1-Butoxyvinyl)-9-methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphthalene-6-ylmethyl toluene-4-sulfonate (47)

To a solution of 46 (78 mg, 0.218 mmol) in MeOH (1 mL) was added 10% NaOH (2 mL) at rt. After being stirred at rt for 30 min, the mixture was diluted with CH$_2$Cl$_2$ and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo to give alcohol (55.4 mg, 81%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 8.05 (1H, s), 7.56 (1H, s), 4.36 (1H, d, $J$ = 2.1 Hz), 4.17 (1H, d, $J$ = 1.8 Hz), 4.00-3.61 (4H, m), 3.55-3.40 (1H, m), 3.40-3.21 (1H, m), 2.35-1.93 (2H, m), 1.90-1.60 (4H, m), 1.48 (3H, d, $J$ = 6.9 Hz), 1.59-1.25 (2H, m), 0.92 (3H, t, $J$ = 7.5 Hz); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 162.4, 152.5, 149.5, 137.9, 135.8, 134.4, 127.2, 119.9, 86.8, 68.1, 65.7, 38.1, 31.2, 29.3, 26.7, 23.8, 22.1, 19.6, 14.0.

To a solution of alcohol (203 mg, 0.644 mmol) in CH$_2$Cl$_2$ (2 mL) were added DMAP (118 mg, 0.966 mmol) and TsCl (147 mg, 0.773 mmol) at rt. After being stirred at rt for 2 h, the mixture was diluted with CH$_2$Cl$_2$ and washed with aqueous citric acid solution. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 10:1 to 7:1) to give 47 (279 mg, 92%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 8.04 (1H, s), 7.73 (2H, d, $J$ = 8.4 Hz), 7.51 (1H, s), 7.29 (2H, d, $J$ = 8.4 Hz), 4.36 (1H, dd, $J$
= 9.6, 4.2 Hz), 4.23 (1H, d, J = 2.1 Hz), 4.02 (1H, d, J = 2.1 Hz), 3.98 (1H, dd, J = 11.1, 9.9 Hz), 3.90-3.60 (3H, m), 3.33-3.12 (1H, m), 2.41 (3H, s), 2.20-1.83 (2H, m), 1.80-1.55 (4H, m), 1.55-1.25 (2H, m), 1.38 (3H, d, J = 6.9 Hz), 0.92 (3H, t, J = 7.5 Hz); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 161.8, 152.7, 149.4, 144.9, 144.9, 138.6, 136.0, 133.3, 131.5, 130.0, 128.2, 127.5, 120.1, 86.9, 71.5, 68.1, 34.8, 31.1, 29.2, 26.0, 23.1, 21.9, 21.8, 19.6, 14.0.

8-Acetyl-6-formylamino-5-hydroxy-4-methyl-1,2,3,4-tetrahydronaphthalen-1-ylmethyl toluene-4-sulfonate (48)

To a solution of 47 (10 mg, 0.021 mmol) in CH$_2$Cl$_2$ (1 mL) was added SnCl$_4$ (1 M solution in CH$_2$Cl$_2$, 21 µL, 0.021 mmol) at -78 °C. After being stirred at -78 °C for 5 min, the mixture was quenched with saturated NaHCO$_3$ solution. The mixture was diluted with CH$_2$Cl$_2$ and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo to give 48 (8 mg, 89%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 9.42 (1H, s), 8.83 (1H, s), 7.67 (2H, d, J = 8.4 Hz), 7.29 (2H, d, J = 8.4 Hz), 4.21 (1H, dd, J = 9.3, 5.4 Hz), 4.12 (1H, dd, J = 9.3, 9.0 Hz), 4.05 (1H, br s), 3.75 (1H, br s), 3.46-3.26 (1H, m), 2.62 (3H, s), 2.42 (3H, s), 2.20-1.35 (4H, m), 1.45 (3H, d, J = 6.9 Hz).

5-Acetyl-9-methyl-6,7,8,9-tetrahydro-1-oxa-3-azacyclopenta[a]naphtalen-6-ylmethyl acetate (49)

A solution of 46 (1 g, 2.8 mmol) in 10% HCl (20 mL) and 1,4-dioxane (10 mL) was stirred at rt for 30 min. The mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo to give intermediate, 8-acetyl-6-formylamino-5-hydroxy-4-methyl-1,2,3,4-tetrahydronaphthalen-1-ylmethyl acetate which was dissolved in benzene and PTSA-H$_2$O (53 mg, 0.28 mmol) was added at rt. The mixture was heated to reflux overnight with the azeotropic removal of H$_2$O.
using a Dean-Stark trap. The mixture was concentrated in vacuo and the residue was purified
by sgc (H:EA = 2:1) to give 49 (632 mg, 75%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 8.11 (1H, s),
7.88 (1H, s), 4.16 (1H, dd, $J = 10.8, 9.3$ Hz), 4.08 (1H, dd, $J = 10.8, 4.5$ Hz), 4.03-3.92 (1H,
m), 3.32-3.16 (1H, m), 2.60 (3H, s), 1.97 (3H, s), 2.02-1.86 (2H, m), 1.72-1.52 (2H, m), 1.48
(3H, d, $J = 6.9$ Hz); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 202.2, 171.0, 153.4, 150.8, 138.0, 136.5,
134.6, 128.7, 119.6, 67.1, 33.4, 30.8, 29.4, 26.3, 23.8, 21.9, 21.2.

1,6-Dimethyl-2,3,3a,4-tetrahydro-1H,6H-5,10-dioxa-8-azacyclopenta[a]phenalen-6-ol
(50)

To a solution of 49 (110 mg, 0.365 mmol) in MeOH (1 mL) was added 10% NaOH (3 mL) was added at rt. After being stirred at rt for 10 min, the mixture was acidified with aqueous citric acid solution at 0 °C. The mixture was diluted with CH$_2$Cl$_2$ and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo to give 50 (93 mg, 98%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 8.05 (1H, s), 7.60 (1H, s), 3.83 (1H, dd, $J =
10.5, 4.8$ Hz), 3.62 (1H, dd, $J = 11.1, 10.8$ Hz), 3.50-3.35 (1H, m), 2.96-2.81 (1H, m), 2.10-
1.30 (4H, m), 1.66 (3H, s), 1.30 (3H, d, $J = 6.9$ Hz); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 152.7,

3',4'-Dihydroxyacetophenone (51)

To a suspension of AlCl$_3$ (18 g, 136.2 mmol) in CH$_2$Cl$_2$ (100 mL) was added catechol (5 g, 45.4 mmol) in one portion at rt. After 5 min, acetyl chloride (3.3 mL, 46.3 mmol) was added to this mixture at rt. After being stirred at rt overnight, the mixture was quenched with cold H$_2$O at 0 °C. The mixture was diluted with Et$_2$O and washed with brine. The first extract contained unreacted starting material (catechol) and product 51. The aqueous layer was extracted with Et$_2$O several times because the product was soluble in H$_2$O. The latter extracts
contained almost pure product 51 (3.2 g, 46%). 300 MHz $^1$H NMR (acetone-d$_6$) δ 8.51 (2H, br s), 7.47 (1H, d, $J$ = 2.1 Hz), 7.44 (1H, dd, $J$ = 8.1, 2.1 Hz), 6.89 (1H, d, $J$ = 8.1 Hz), 2.46 (3H, s).

3',4'-Bis(tert-butyldimethylsilyloxy)acetophenone (52)

To a solution of 51 (118 mg, 0.776 mmol) in DMF (2 mL) were added imidazole (116 mg, 1.71 mmol) and TBSCl (257 mg, 1.71 mmol) at rt. After being stirred at rt overnight, the mixture was diluted with ethyl acetate and washed with H$_2$O three times. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 50:1) to give 52 (295 mg, 100%). 300 MHz $^1$H NMR (CDCl$_3$) δ 7.50-7.42 (2H, m), 6.85 (1H, d, $J$ = 9.0 Hz), 2.52 (3H, s), 1.00 (9H, s), 0.99 (9H, s), 0.24 (6H, s), 0.23 (6H, s).

1-[3,4-Bis(tert-butyldimethylsilyloxy)phenyl]-3-hydroxyocta-4,6-dien-1-one (53)

To a solution of 52 (746 mg, 1.96 mmol) in THF (6.5 mL) was added t-BuOK (264 mg, 2.35 mmol) at 0 °C. After 5 min, 2,4-hexadienal (216 µL, 1.96 mmol) was added to this mixture at 0 °C. After being stirred at 0 °C for 5 min, the mixture was quenched with 10% HCl at 0 °C. The mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 20:1 to 10:1) to give 53 (607 mg, 65%). 300 MHz $^1$H NMR (CDCl$_3$) δ 7.50-7.42 (2H, m), 6.85 (1H, d, $J$ = 9.0 Hz), 6.29 (1H, dd, $J$ = 15.0, 10.5 Hz), 6.05 (1H, dd, $J$ = 15.0, 10.5 Hz), 5.82-5.70 (1H, m), 5.64 (1H, dd, $J$ = 15.3, 6.3 Hz), 4.74 (1H, t, $J$ = 8.1 Hz), 3.41 (1H, br s), 3.22-2.98 (2H, m), 1.75 (3H, d, $J$ = 6.9 Hz), 1.00 (9H, s), 0.99 (9H, s), 0.24 (6H, s), 0.23 (6H, s).

1-{2-[3,4-Bis(tert-butyldimethylsilyloxy)phenyl]-2-oxoethyl}hexa-2,4-dienyl acetate (54)
To a solution of 53 (65 mg, 0.136 mmol) in CH$_2$Cl$_2$ (1 mL) were added DMAP (18 mg, 0.15 mmol) and Ac$_2$O (14 µL, 0.15 mmol) at rt. After being stirred at rt for 2 h, the mixture was diluted with ethyl acetate and washed with aqueous citric acid solution, saturated NaHCO$_3$ solution, and brine, successively. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo to give 54 (67.6 mg, 96%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.50-7.42 (2H, m), 6.85 (1H, d, $J$ = 9.0 Hz), 6.27 (1H, dd, $J$ = 15.0, 10.5 Hz), 6.00 (1H, dd, $J$ = 15.0, 10.5 Hz), 5.94-5.64 (2H, m), 5.58 (1H, dd, $J$ = 15.3, 6.3 Hz), 3.35 (1H, dd, $J$ = 16.5, 7.5 Hz), 3.05 (1H, dd, $J$ = 16.5, 6.0 Hz), 2.01 (3H, s), 1.74 (3H, d, $J$ = 6.9 Hz), 1.00 (9H, s), 0.99 (9H, s), 0.24 (6H, s), 0.23 (6H, s).

1-(3,4-Dihydroxyphenyl)octa-2,4,6-trien-1-one (55)

To a solution of 53 or 54 in CH$_3$CN was added 49% HF (2 equivalent) at 0 °C. After being stirred at rt overnight, the mixture was concentrated in vacuo. The residue was purified by sgc (H:EA = 2:1) to give 55 and/or 51. Alternatively, 53 was treated with PTSA-H$_2$O in benzene to give 55. 300 MHz $^1$H NMR (acetone-d$_6$) $\delta$ 8.55 (2H, br s), 7.53 (1H, d, $J$ = 2.1 Hz), 7.50 (1H, dd, $J$ = 8.1, 2.1 Hz), 7.36 (1H, dd, $J$ = 14.7, 11.1 Hz), 7.14 (1H, d, $J$ = 14.7 Hz), 6.91 (1H, d, $J$ = 8.1 Hz), 6.73 (1H, dd, $J$ = 14.7, 10.2 Hz), 6.45 (1H, dd, $J$ = 15.0, 11.4 Hz), 6.26 (1H, dd, $J$ = 15.0, 10.5 Hz), 6.10-5.95 (1H, m), 1.81 (3H, d, $J$ = 6.9 Hz).

1-(3,4-Dihydroxyphenyl)-3-hydroxyocta-4,6-dien-1-one (56)

To a solution of diisopropylamine (3.7 mL, 26.28 mmol) in THF (20 mL) was added n-BuLi (2.5 M solution in hexanes, 10.5 mL, 26.28 mmol) at 0 °C. After 5 min, HMPA (4.6 mL, 26.28 mmol) was added to this mixture at 0 °C. After 5 min, a solution of 51 (1 g, 6.57 mmol) in THF (5 mL + 5 mL for rinse) was transferred to this mixture at 0 °C via cannula. After 5 min, a solution of 2,4-hexadienal (725 µL, 6.57 mmol) in THF (3 mL) was added to
this at 0 °C via cannula. After 10 min, the mixture was quenched with aqueous citric acid solution (pH was adjusted to 5 or 6). The mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 2:1 to 1:1) to afford 56 (1.305 g, 80%). 400 MHz ¹H NMR (CDCl₃) δ 7.83 (1H, br s), 7.62 (1H, br s), 7.43 (1H, s), 7.30 (1H, d, J = 8.4 Hz), 6.78 (1H, d, J = 8.4 Hz), 6.19 (1H, dd, J = 15.2, 10.4 Hz), 5.93 (1H, dd, J = 15.2, 10.4 Hz), 5.72-5.60 (1H, m), 5.57 (1H, dd, J = 15.2, 6.8 Hz), 4.77 (1H, br s), 4.32 (1H, br s), 3.12 (1H, dd, J = 17.2, 8.8 Hz), 3.01 (1H, dd, J = 17.2, 2.8 Hz), 1.68 (3H, d, J = 6.9 Hz).

**Methyl 4-hydroxymandelate (57)**

To a solution of 4-hydroxymandelic acid monohydrate (820 mg, 4.4 mmol) in THF (8 mL) was added a solution of diazomethane in Et₂O at 0 °C until the color of the reaction mixture maintained yellow. After the mixture was stirred at 0 °C for 5 min, the excess diazomethane was quenched with AcOH at 0 °C. The mixture was concentrated in vacuo to give ester 57 (802 mg, 100%). 300 MHz ¹H NMR (CDCl₃) δ 7.28 (2H, d, 8.4 Hz), 6.82 (2H, d, J = 8.4 Hz), 5.12 (1H, d, J = 5.7 Hz), 4.88 (1H, br s), 3.76 (3H, s), 3.35 (1H, d, J = 5.7 Hz).

**3-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)octa-4,6-dien-1-one (58)**

To a solution of diisopropylamine (422 µL, 3 mmol) in THF (1.5 mL) was added n-BuLi (2.5 M solution in hexanes, 1.2 mL, 3 mmol) at –78 °C. After 5 min at rt, the mixture was recooled to –78 °C. To this mixture was transferred a solution of acetovanillone (200 mg, 1.2 mmol) in THF (1 mL + 1 mL for rinse) at –78 °C. After 5 min, a solution of 2,4-hexadienal (132 µL, 1.2 mmol) in THF (1 mL) was added to this at –78 °C via cannula. After being stirred at –78 °C for 10 min, the mixture was quenched with AcOH at –78 °C. The mixture
was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 3:1) to give 58 (230 mg, 73%). 300 MHz ¹H NMR (CDCl₃) δ 7.59-7.47 (2H, m), 6.95 (1H, d, J = 8.4 Hz), 6.29 (1H, dd, J = 15.3, 10.5 Hz), 6.23 (1H, br s), 6.05 (1H, dd, J = 15.3, 10.5 Hz), 5.82-5.68 (1H, m), 5.64 (1H, dd, J = 15.3, 6.3 Hz), 4.83-4.70 (1H, m), 3.94 (3H, s), 3.23-3.03 (2H, m), 1.73 (3H, d, J = 6.9 Hz), 1.70 (1H, br s).

1-(4-Hydroxy-3-methoxyphenyl)octa-4,6-diene-1,3-diol (59)

To a solution of 58 (56.3 mg, 0.215 mmol) in THF (2 mL) was added LAH (24 mg, 0.645 mmol) at 0 °C. After being stirred at 0 °C for 5 min, the mixture was quenched with H₂O and stirred for 30 min. The mixture was filtered through Celite and rinsed with ethyl acetate. The filtrate was evaporated in vacuo to afford 59 (8.5 mg, 15%). 300 MHz ¹H NMR (acetone-d₆) δ 6.95 (1H, d, J = 2.1 Hz), 6.78 (1H, dd, J = 8.4, 2.1 Hz), 6.71 (1H, d, J = 8.4 Hz), 6.25-6.11 (1H, m), 6.11-5.95 (1H, m), 5.73-5.51 (2H, m), 4.90-4.72 (1H, m), 4.40-4.28 (1H, m), 3.79 (3H, s), 3.20-2.60 (5H, br s), 1.71 (3H, d, J = 6.9 Hz).

6-Methoxy-4-methyl-5,8-dioxo-1,4,5,8-tetrahydronaphthalen-1-ylmethyl acetate (60a), 7-Methoxy-4-methyl-5,8-dioxo-1,4,5,8-tetrahydronaphthalen-1-ylmethyl acetate (60b), 5,8-Dihydroxy-6-methyl-1,4-dihydronaphthalen-1-ylmethyl acetate (61a), and 5,8-Dihydroxy-7-methoxy-4-methyl-1,4-dihydronaphthalen-1-ylmethyl acetate (61b)

A mixture of methoxy-1,4-benzoquinone (66 mg, 0.476 mmol) and 3 (80 mg, 0.571 mmol) in CH₂CN (2 mL) and H₂O (0.4 mL) was heated to reflux overnight. After the solvent was evaporated in vacuo, the residue was purified by sgc (H:EA = 2:1) to give 60a/b and 61a/b.

60a/b: 300 MHz ¹H NMR (CDCl₃) δ 6.78-5.33 (3H, m), 4.46-3.95 (2H, m), 3.95-3.35 (5H,
m), 2.12-1.92 (3H, m), 1.35-1.15 (3H, m).

**61a/b**: 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 6.50-5.25 (5H, m), 4.49-3.90 (2H, m), 3.89-2.58 (5H, m), 2.17-1.92 (3H, m), 1.35-0.70 (3H, m).

**5-Hydroxymethyl-8-methyl-5,8-dihydrornaphthalene-1,4-diol (63)**

A mixture of 1,4-benzoquinone (1 g, 9.25 mmol) and 2,4-hexadienol (999 mg, 10.18 mmol) in benzene (20 mL) was heated to reflux overnight. After the solvent was evaporated in vacuo, the residue was purified by sgc (H:EA = 5:1 to 2:1) to give 63 (954 mg, 50%). 300 MHz $^1$H NMR (acetone-d$_6$) $\delta$ 8.19 (IH, br s), 7.71 (2H, br s), 6.60 (1H, d, $J = 8.7$ Hz), 6.55 (1H, d, $J = 8.7$ Hz), 6.03 (1H, dd, $J = 9.9, 5.1$ Hz), 5.90 (1H, dd, $J = 9.9, 4.5$ Hz), 3.85-3.70 (2H, m), 3.70-3.55 (2H, m), 1.23 (3H, d, $J = 6.9$ Hz).

**5-Hydroxymethyl-8-methyl-5,8-dihydro[1,4]naphthoquinone (62)**

To a solution of 63 (928 mg, 4.5 mmol) in benzene (10 mL) and ethyl acetate (10 mL) were added Na$_2$SO$_4$ (1.34 g, 9.45 mmol) and Ag$_2$O (2.1 g, 9 mmol) at rt. The reaction flask was covered with aluminum foil. After being stirred at rt overnight, the mixture was filtered through Celite and rinsed with ethyl acetate. The filtrate was evaporated in vacuo and the residue was purified by sgc (H:EA = 3:1 to 2:1) to give 62 (569 mg, 62%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 6.71 (2H, s), 5.97 (1H, dd, $J = 9.6, 4.2$ Hz), 5.73 (1H, dd, $J = 9.6, 4.2$ Hz), 3.71 (1H, dd, $J = 10.5, 4.5$ Hz), 3.63 (1H, dd, $J = 10.8, 4.5$ Hz), 3.59-3.48 (1H, m), 3.48-3.33 (1H, m), 2.14 (1H, br s), 1.21 (3H, d, $J = 6.9$ Hz).

**2-Amino-5-hydroxymethyl-8-methyl-5,8-dihydro[1,4]naphthoquinone and 2-Amino-8-hydroxymethyl-5-methyl-5,8-dihydro[1,4]naphthoquinone (64)**

To a solution of MeONH$_2$-HCl (38 mg, 0.451 mmol) in EtOH (1 mL) was added Et$_3$N (63 $\mu$L, 0.451 mmol) at 0 °C. To this mixture was dropwise added a solution of 62 (92 mg,
0.451 mmol) in EtOH (1 mL + 1 mL for rinse) at 0 °C. After being stirred at rt overnight, the mixture was concentrated in vacuo, the residue was diluted with ethyl acetate, and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by sgc (H:EA = 2:1 to 1:1) to give 64 (69.2 mg, 70%) as a mixture of 3:1 regioisomers. 300 MHz ¹H NMR (CDCl₃) δ 6.05-5.90 (1H, m), 5.80-5.65 (2H, m), 5.13 and 5.02 (2H, br s), 3.82-3.31 (4H, m), 2.75 (1H, br s), 1.24 and 1.23 (3H, d, J = 6.9 Hz).

References

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GENERAL CONCLUSIONS

In this dissertation, we have investigated direct routes to several biologically active natural products.

Chapter 1 described a concise construction of core skeleton of malibatol A, employing a novel benzofuran formation methodology and a regio- and stereoselective 7-membered ring formation via Lewis acid catalyzed epoxide ring opening as crucial steps.

Chapter 2 described direct approaches to isoflavanquinones utilizing radical addition to quinones. Three main strategies were presented and were compared to generate radicals from the corresponding precursors.

Chapter 3 described a direct entry to erogorgiaene, naturally occurring potent antitubercular agent, featuring a regioselective metal-halogen exchange and a 6-exo-trig radical cyclization as key transformations.

Chapter 4 described synthetic studies towards antitubercular benzoxazole alkaloids. The core tricyclic skeleton of the originally proposed structures of these natural products was synthesized using an intermolecular Diels-Alder reaction as a key step.
ACKNOWLEDGEMENTS

First, I would like to express my sincere gratitude to my advisor, Dr. George A. Kraus for his invaluable guidance and constant encouragement for the projects in which I've been involved. Without his advice and support, this Ph.D. work would have been impossible.

Thanks are also extended to Dr. Richard C. Larock, Dr. Nicola L. Pohl, Dr. Jacob W. Petrich, and Dr. Earl G. Hammond, members of my study committee for their help and guidance during my study at Iowa State University.

My appreciation goes to the past and present Kraus group members with whom I have worked for the last three and a half years.

I am also grateful to my parents-in-law for their continuing support and encouragement. I am deeply indebted to my two sisters and their families for their love and trust. My special and heartfelt thanks go to my wife, Minyoung for her love, patience, sacrifice, and understanding. I would like to thank my son, Joowan for providing me the reason to smile all the time. I give my deepest appreciation and thanks to my late parents for making me who I am. Without their unyielding love and sacrifice, my life would not have come here.

Finally, I would like to thank my God who always guides me in the right direction.